ARCHIVES OF OPHTHALMOLOGY

VOLUME 32 (old series volume 89) OCTOBER 1944 NUMBER 4

COPYRIGHT, 1944, BY THE AMERICAN MEDICAL ASSOCIATION

LOCALIZATION OF INTRAOCULAR FOREIGN BODIES BY MEANS OF THE CONTACT LENS

RAYMOND L. PFEIFFER, M.D.

NEW YORK

The war and the war industries make the consideration of the treatment of intraocular foreign bodies opportune. Surgeons who heretofore have had little experience with intraocular foreign bodies are being called on to treat many injuries of this type. Roentgenologists likewise are feeling more poignantly their responsibility in this field. Naturally the question arises as to which methods of treatment are superior. After the use of various technics, I have found the procedures here described best adapted to the problem.

The choice of surgical procedure for the extraction of foreign bodies seems to be changing. Many surgeons with much experience in the handling of intraocular injuries are giving up the use of the giant magnet entirely, and others use it only in rare instances. The grosser technic of the giant magnet has not satisfied the surgeons' desire for refinement and has failed to produce results comparable to those achieved with the hand instrument. Success with the hand magnet, however, depends on accurate localization of the foreign body, so that it may be removed directly through the wall of the eye with a minimum of injury. Precise localization, therefore, is imperative.

Many methods for both localization and removal of intraocular fragments are available, and no unanimity of opinion on the superiority of this or that method exists, though it is probable that certain technics are definitely superior. There is no doubt, however, that ophthalmologists are dependent on roentgen examination for the diagnosis and localization of intraocular bodies. Although ophthalmoscopy is frequently of great value, it cannot be employed as a substitute for roentgen localization, even when the foreign fragment can be seen with an ophthalmoscope. It is not possible to locate a foreign body with the ophthalmoscope as accurately as by roentgen examination. Ophthalmoscopy is a valuable adjunct and should be used in every case in addition to roentgen examination but not to replace it. With consummate care it is possible for a roentgenologist to localize a foreign fragment in the eye and to give the points of its position with greater accuracy than the surgeon can utilize at operation.

Unless the surgeon is careful the value of the good work of the roentgenologist may be lost. In applying the data on the position of the body in the eye the operator should mark the exact meridian in which the body lies with peripheral scratches on the cornea, stained with fluorescein, before making an incision. In locating the meridian, a Guist protractor is an important aid. If reliable localization is not available, the Berman locator may be used to determine the site for the incision if the particle is of iron or steel. If the fragment is far posterior and the meridian in which the fragment lies is difficult to trace posteriorly from the cornea, this remarkable instrument should be most helpful.

Ophthalmologists have generally assumed that the localization of intraocular particles is a task for the roentgenologist. In some communities the roentgenologists are so engrossed in general work that they have little interest in what may appear to be an annoying and trifling problem. With the methods to be presently described, an ophthalmic surgeon does not need to be altogether dependent on a roentgenologist. He should be equipped to take patients to an x-ray laboratory and prepared to direct the procedure. Certainly every recent graduate in ophthalmology should be able to locate intraocular fragments with complete assurance.

In every case of possible intraocular foreign body, bone-free roentgenograms should be made by Vogt's method (fig. 1).[1] Roentgenograms made by this method show far more than those made with rays which penetrate the bones of the skull, and they reveal bodies of almost any density greater than that of the soft tissues. Small

Read before the Academy of Medicine, New York, Dec. 20, 1943.

From the Institute of Ophthalmology, Presbyterian Hospital, and the Department of Ophthalmology, College of Physicians and Surgeons, Columbia University.

1. (*a*) Vogt, A.: Skelettfreie Röntgenaufnahme des vorderen Bulbusabschnittes, Schweiz. med. Wchnschr. **51**:145, 1921; (*b*) Weitere Beobachtungen über skelettfreie Röntgenaufnahme des vordern Bulbusabschnittes, ibid. **4**:982, 1923.

fragments of glass and minute metallic bodies whose shadows are lost in the grain of films exposed in the ordinary way can be shown. Bone-free roentgenograms are also valuable for determining the exact size and shape of bodies that have been localized on films exposed in the regular way. The more prominent the eye, the more useful is this method. An ordinary dental film is held over and perpendicular to the inner canthus of the eye, and the rays are directed from the side so that a shadow of the profile of the anterior segment of the eye, which includes the eyelids, the cornea and portions of the sclera, is recorded on the film. This method is useful

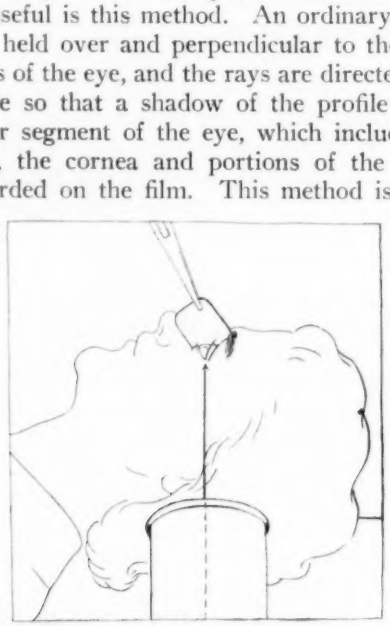

Fig. 1.—A drawing showing the position of the dental film held over the inner canthus for the production of a bone-free roentgenogram of the anterior segment of the eye.

only for localizing fragments in the anterior 8 to 12 mm. of the eye. Although the procedure is used primarily for diagnosis, it may be employed to localize foreign bodies by directing the rays from various angles onto dental films marked with pencil lines alined with the limbus or the apex of the cornea. The position of the body is noted with reference to the lines on the roentgenograms, the shadow of the limbus or of the apex of the cornea and the angle at which the rays were directed toward the films.

All mechanical devices available for use in roentgen examination to determine the position of a foreign body in the eye use as a point of reference some definite part of the anterior segment, either the apex of the cornea or the plane of the limbus of the cornea. For this reason a fragment localized in or on the posterior sclera may be either in or out of the eyeball, depending on the size of the eyeball. A knowledge of the refraction of the eye is helpful. The position may be determined by injecting air into Tenon's capsule [2] and exposing films in such a manner that the rays pass in a line tangential to the sclera adjacent to the point at which the foreign body is known to lie.

Eyes in which more than one fragment is found pose a particularly difficult problem. Several pellets of equal size and shape may be impossible to differentiate and localize.

The method of localization of foreign bodies which is probably superior to all others is that which employs the contact lens (fig. 2). The technic of this method is simple. It provides two roentgenograms, a posteroanterior and a lateral, which permit a meridional report, which is the easiest for the surgeon to use when operating. The method of localization is rapid, requires a minimum of apparatus and is applicable in all cases. Its outstanding advantage, however, is accuracy. It achieves a degree of accuracy which cannot be approached by five other methods with which I have had experience. It is not possible to make a gross error with this method; in all instances in which the contact lens fits the eye, the body is localized precisely, not just within a few millimeters, which is the margin of error claimed for most of the other methods. It seems safe to predict that in the course of time this method will replace all others.

Comberg [3] in 1927 adapted the Zeiss contact lens for the localization of foreign bodies. Prior to that date Wessely [4] used a glass prosthesis with tinfoil markers and later a crystal prosthesis that fitted on the eyeball. These prostheses, however, gave only a clue to the position of the globe, because they did not fit the eye well or

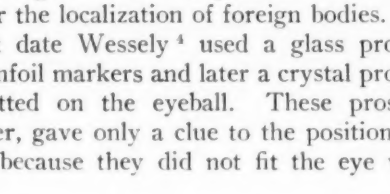

Fig. 2.—The contact lens especially adapted for roentgenographic localization of intraocular foreign bodies by the addition of four radiopaque markers (from Pfeiffer [6]).

2. Spackman, E. W.: X-Ray Diagnosis of Double Perforation of Eyeball After Injection of Air into the Space of Tenon, Am. J. Ophth. **15**:1007, 1932.

3. (*a*) Comberg, W.: Ein neues Verfahren zur Röntbenlokalization am Augapfel, Arch. f. Ophth. **118**: 175, 1927; (*b*) Ein Hilfsgerät für mein Verfahren der Röntgenlokalization und einige Bemerkungen über die Technik, ibid. **124**:665, 1930.

4. (*a*) Wessely, K.: Verfahren zur Lokalisation von metalischen intraocularen Fremdkörpern im Röntgenbilde, Ztschr. f. Augenh., 1910, vol. 24; (*b*) Ein Verfahren zur Kenntlichmachung der Bulbusoberfläche und der Hornhaut im Röntgenbilde zwecks Lokalisierung von intraokularen Fremdkörpern, Arch. f. Augenh. **69**: 161, 1911.

follow its movements. Later they were sewed to the conjunctiva, and other disadvantages were thus introduced. Then Engelbrecht [5] designated the cornea with balls of celluloid with wire crosses, which answered most requirements successfully. The contact glass of Comberg, in which the limbus of the cornea is designated by lead markers, fits tightly and moves with the eye. It is a lens of the type used for the correction of visual defects, and if the central visual acuity of the injured eye is not disturbed it is possible for the eye to fixate with the prosthesis in place. A lens of average size is used, that is, one with a

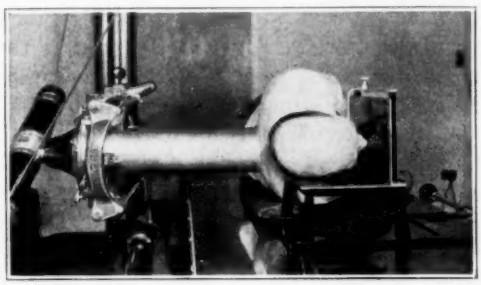

Fig. 3.—The arrangement of the apparatus for the posteroanterior exposure. The patient is in position, with the contact lens on the right eye. Note the perfect lateral position of the patient's head, with the chin and nose against the vertical tunnel. Immobilization is gained by biting a bar attached to the L-shaped device. (From Pfeiffer.[6])

radius of 12 mm. for the scleral curve and of 8 mm. for the corneal curve. The lens may be inserted and removed with ease. When it has been sterilized, it may be used on a lacerated globe with impunity. Lenses of this type are manufactured in the United States of plastic material.

Two roentgen exposures are made, a lateral and an anteroposterior. Lines are drawn on the films to show the relationship of the foreign particle to the contact lens. The location is then indicated on charts that represent an anteroposterior view of the eye and a cross section cut in the meridian in which the foreign body lies.

In order to shorten the time required for the projections and to remove one source of error, I have adapted a special device, which is not, however, indispensable to the method.[6] The device consists of an L-shaped arrangement of tunnels to hold the cassettes; with this device the patient's head may be maintained in one position and the position of the tube changed between the two exposures.

PROCEDURE OF OBTAINING THE ROENTGENOGRAMS

The eye containing the intraocular foreign body is anesthetized with several drops of 0.5 per cent solution of tetracaine hydrochloride. The patient is directed to look down, and the contact lens is inserted by slipping the glass under the upper lid and lifting the lower lid. The lens finds its proper position over the cornea.

Two exposures are made, a posteroanterior and a lateral. The L-shaped device is placed on the roentgenographic table, and the positions of the tube for the two exposures are determined (fig. 3). In both positions the primary rays are directed perpendicular to the surface of a tunnel so that they pass through the eye containing the foreign body. The target-film distance is the same for each exposure; a distance of 35 to 40 inches (90 to 100 cm.) should be used.

The exposure for the posteroanterior view is made first. A patient with a foreign body in the right eye is instructed to lie on the table on his

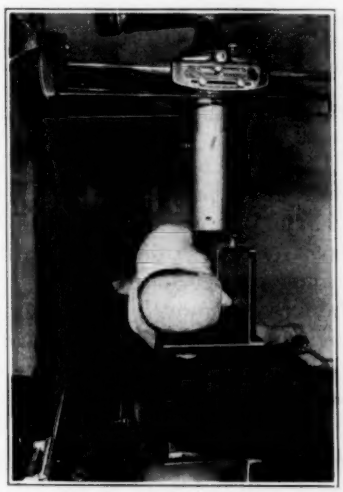

Fig. 4.—The arrangement of the apparatus for the right lateral exposure; the film is placed in the horizontal tunnel. Note the alinement of the tube with the right orbit. The position of the contact lens can be checked through the apertures in the vertical tunnel. (From Pfeiffer.[6])

right side, with the right side of the head on the horizontal tunnel of the device. The tube is alined in the horizontal position (fig. 3). The head is placed so that the sagittal plane is horizontal and the injured eye is opposite the lower opening in the vertical tunnel. Through the opening in the vertical tunnel the position of the contact lens on the eye is checked, and the glass

5. Engelbrecht, in Hoffmann, W.: Die Röntgendiagnostik und Therapie in der Augenheilkunde, Radiologische praktika, Leipzig, Georg Thieme, 1932, vol. 19.

6. Pfeiffer, R. L.: Localization of Intraocular Foreign Bodies with the Contact Lens, Am. J. Roentgenol. **44**:558, 1940.

is rotated to place the markers in the vertical and horizontal planes. The patient is asked to gaze directly forward and to hold this position. To immobilize the head the patient may bite a bar attached to the L-shaped device. The position of the tube is checked; the cassette is placed in position in the vertical tunnel, and the posteroanterior exposure is made.

With the patient in the same position the tube is alined vertically and centered over the patient's eye for the lateral view (fig. 4). The cassette is placed in the horizontal tunnel, under the

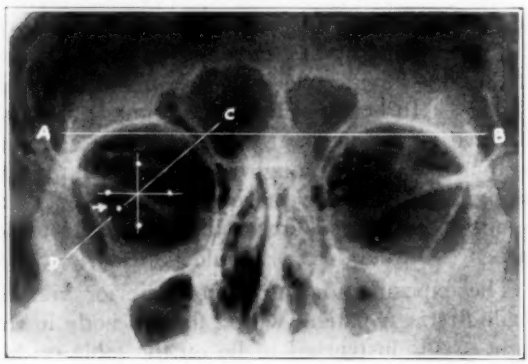

Fig. 5.—Roentgenogram of an intraorbital foreign body, posteroanterior view, with lines drawn as described in the text. The long diagonal line *CD*, which passes through the center of the lens and the foreign body, indicates the meridian in which the body lies. The meridian is determined with the aid of line *AB* across the orbits.

patient's head; the position of the contact lens is checked, and the second exposure is made. The patient is then permitted to sit in a chair while the films are developed. If they are satisfactory, the lens is removed. This is done easily by inserting a blunt hook or a tooth stick applicator under the lower edge of the lens while the patient looks up. A special rubber sucker may be used for inserting and removing the lens.

For the localization of a foreign body in the left eye the device is placed at the other end of the table, the patient lies on his left side and the procedure just described is followed.

Stereoscopic films of the head in the lateral or Caldwell position may be made to determine the presence of a foreign body before localization is undertaken. Cassettes with fine grain screens are used, and the exposures are made slightly less dense than for sinuses.

METHOD OF PLOTTING THE POSITION OF THE FOREIGN BODY

The film of the posteroanterior view is placed in the viewing box, and a horizontal line is drawn or scratched across the orbits several millimeters below the upper margins (fig. 5, line *AB*). A horizontal and a vertical line are scratched through the shadows of the markers on the contact lens to locate its center. A longer line (*CD*) is then drawn to bisect the foreign body and pass through the center of the lens. The angle formed by this line (*CD*) with the horizontal line through the upper part of the orbit (*AB*) is measured with a protractor and a corresponding line (*C'D'*) at this angle is plotted on a chart representing the front view of the eye (fig. 7). Then with a compass and millimeter rule, the distance of the foreign particle from the center of the contact glass is measured. This measurement minus a correction for the magnification of the lens on the film is transferred to the chart. The corrected measurement represents the distance of the foreign body from the anteroposterior axis of the eyeball. The size of the correction factor depends on several variables in the technic. The contact lens is 20 mm. in diameter, but on the film it may measure 22 mm. The error then is one tenth of the distance measured on the film. The actual dis-

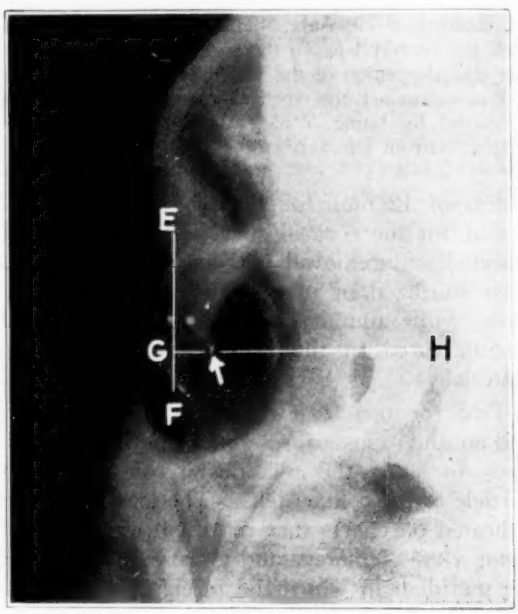

Fig. 6.—Lateral view of an intraocular foreign body, with a line drawn anterior to the markers to indicate the plane of the limbus (*EF*). *GH* is drawn vertical to *EF* and through the foreign body, which is indicated by an arrow.

tance of the foreign body from the axis of the eyeball (X) may be derived from the equation:

Actual diameter of contact glass: Diameter of contact glass on the film ⁀ X: distance of foreign body from axis of eyeball on the film.

In placing the posteroanterior roentgenogram in the viewing box for measuring, care should

be taken to see that it is viewed as an antero-posterior picture, that is, with the right orbit on the left side, as though the patient were being examined directly. The nasal or the temporal side of the eye should be carefully labeled on the chart of the front view (fig. 7). This information facilitates interpretation by the surgeon.

The film showing the lateral view (fig. 6) is then placed in the viewing box and a line (EF) is drawn across the shadow of the contact lens, anterior and tangential to the markers of the lens, to locate the limbus of the cornea. A second line (GH) is drawn perpendicular to the first through the foreign body. A measurement is then taken along the second line from the foreign body to the plane of the limbus. This measurement corrected for magnification represents the actual distance of the foreign body posterior to the plane of the limbus. The location is then plotted on a chart representing a meridional section of the eyeball. A line ($G'H'$) is drawn across the chart parallel with the limbus at the depth calculated. A second line ($I'J'$) is drawn perpendicular to the first to represent the distance of the foreign body from the axis of the eyeball, which was determined previously. The point at which the two lines cross marks the position of the foreign body in a section of the eyeball at the meridian indicated in the chart of the front view. The charts are made three times the normal size of the eye to increase the accuracy in plotting.

SOURCES OF ERROR

The method of localizing intraocular foreign bodies by the use of a contact lens is probably the most accurate technic, for the markers in relation to which the foreign particle is localized rest directly on the eyeball and accurately indicate the position of the eye. Accuracy is gained too by using the plane of the limbus rather than the apex of the cornea as the point of reference in plotting the position of the foregn body. The two films reveal all the information needed for the plotting, and it is scarcely possible to make a significant error. From the roentgenograms one can tell whether the procedure was performed correctly. Chance superimposition of the foreign particle and a marker of the contact lens in the posteroanterior roentgenogram is not

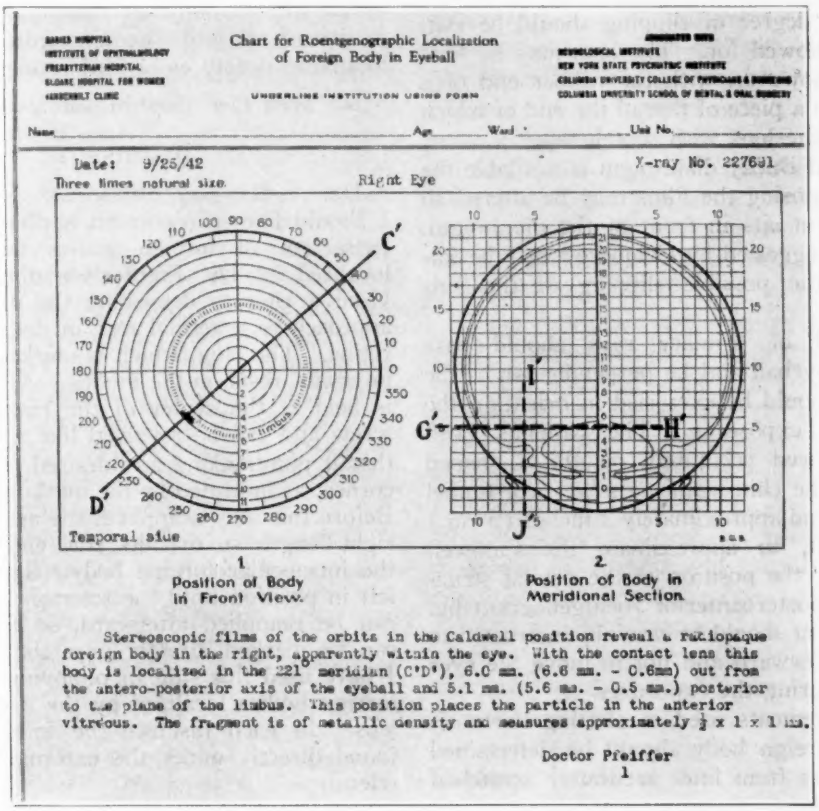
Chart for Roentgenographic Localization
of Foreign Body in Eyeball
UNDERLINE INSTITUTION USING FORM
Name
Age
Ward
Unit No.
Date: 9/25/42
X-ray No. 227691
Three times natural size.
Right Eye
C'
D'
Limbus
I'
J'
G'
H'
Temporal side
1
Position of Body
in Front View.
2
Position of Body in
Meridional Section.
Stereoscopic films of the orbits in the Caldwell position reveal a radiopaque foreign body in the right, apparently within the eye. With the contact lens this body is localized in the 221° meridian (C'D'), 6.0 mm. (6.6 mm. - 0.6mm) out from the antero-posterior axis of the eyeball and 5.1 mm. (5.6 mm. - 0.5 mm.) posterior to the plane of the limbus. This position places the particle in the anterior vitreous. The fragment is of metallic density and measures approximately ½ x 1 x 1 mm.
Doctor Pfeiffer
1

Fig. 7.—Form on which the location of a foreign body is recorded, including the diagnostic report and charts showing the position of the foreign body as seen in a front view and in a meridional section. In the meridional section the position of the body is at the point at which lines $I'J'$ and $G'H'$ cross.

misleading, for the relationship is revealed in the lateral views. Objections to the use of screens scarcely apply to the present day fine grain screens, which give excellent detail. Nothing is to be gained by using film holders.

There is, however, one source of error that may prove disconcerting. It is apparent that one contact lens will not fit all eyes, since eyeballs vary greatly in size and curvature. A lens of average size is used, and fair fitting is usually attained. Frequently there is a tendency for the lens to gravitate downward and thus to leave the curves of the cornea and the sclera. If this happens, the degree of slipping should be estimated and allowed for. The lens may be held in position, however, with the rubber end of a pencil or with a piece of thread the end of which is affixed to the lens with scotch tape.

If a vertical Bucky diaphragm is available the method of exposing the films may be altered so that the patient sits in front of the diaphragm. The technic suggested by Comberg [8] may be followed, and the possible slipping of the lens obviated.

The pencil of primary rays should pass through the eyeball and be perpendicular to the film. Care should be exercised in orienting the tube for the exposures. The patient's head should be placed accurately on the L-shaped device, with the chin against the vertical tunnel and the forehead approximately 2 inches (5 cm.) away from it, to approximate the Caldwell position (note the position of the orbital structures on the posteroanterior roentgenogram fig. 5). The patient should be carefully instructed to gaze directly forward and not to move the eyes or the head during the exposures.

The measurements used in plotting the position of the foreign body should be determined with a compass from lines accurately scratched on the films, and the meridian in which the body lies should be determined with a transparent protractor.

CONCLUSION

Roentgenographic localization of radiopaque intraocular foreign bodies with the aid of the contact glass of Comberg is accurate, simple, easy to perform, adaptable and requires a minimum of apparatus. A meridional graph of the location, derived from the roentgenograms, is achieved. Bone-free roentgenograms of every patient suspected of having an intraocular foreign body are recommended. The injection of air into Tenon's capsule is helpful in localizing deeply embedded foreign bodies.

635 West One Hundred and Sixty-Fifth Street.

DISCUSSION

DR. A. RUSSELL SHERMAN, Newark, N. J.: I should like to report an additional aid in the extraction of foreign bodies that have been localized by Dr. Pfeiffer's method. Guist devised a ring to determine the external site of approach to a retinal tear in detachment of the retina. The ring, which is marked at 10 degree intervals, rests on the limbus. A soft metal arm is held at the center of the ring by a thumbscrew and can be revolved like a clock hand so that it points along any desired meridian of the cornea, as indicated by the markings on the ring. Before the ring is applied, the arm is cut to the right length so that its free end will lie over the intraocular foreign body. The ring can be left in position until the sclera is exposed; or it can be reapplied afterward, so that the sclera can be marked directly over the foreign body. I have used this ring in removing 4 intraocular foreign bodies localized by the use of a contact lens. In each instance the foreign body was found directly under the external mark on the sclera.

CLASSIFICATION OF THE ARTERIOSCLEROTIC-HYPERTENSIVE FUNDUS OCULI IN PATIENTS TREATED WITH SYMPATHECTOMY

LIEUTENANT JEROME A. GANS

MEDICAL CORPS, ARMY OF THE UNITED STATES

Considerable impetus was given to the study of hypertension when Goldblatt [1] showed that persistent hypertension could be produced experimentally in dogs by partial clamping of the renal artery. The years that followed brought an extensive literature, based on a renal origin of hypertension. Page [2] showed that persistent hypertension could also be induced by enclosing the kidney in a sac of cellophane, which produced a constricting capsule of scar tissue. The "ischemic" kidney was shown to contain increased amounts of a substance, renin,[3] which combined in the circulation with a renin activator to produce angiotonin, a pressor substance.[4] Then it was found that normal kidney tissue contained an antipressor substance that inactivated angiotonin; this was used by Page and associates [5] to treat hypertensive patients and experimental animals. Thus, various humoral factors and antifactors have come to light.

A different point of view was presented when Heymans [6] showed that persistent hypertension could be produced neurologically by bilateral excision of the carotid sinus and bilateral section of the cardioinhibitor fibers of the vagus nerve. Reinvestigation of the cold pressor and psychopressor responses has emphasized the nervous mechanisms in hypertension, more particularly since sympathectomy was introduced as therapy. An endocrine basis for hypertension has also been the subject of investigation, especially with respect to the pituitary, thyroid and adrenals, but study along these lines has not been fruitful as yet.

There has been uniform agreement among most investigators concerning the prime importance of the ocular fundus in hypertension, and, accordingly, its status has figured prominently in most studies. From time to time, however, the objection arose that the ocular fundus does not necessarily mirror the condition in other vascular beds of the body. Indeed, there is no evidence that spastic and sclerotic processes in different vascular beds of the body must always keep pace with one another. Another shortcoming may have been the failure to recognize the features of the fundus picture that were pertinent and to separate them from those of lesser significance. More critical examination of the intricate details of the fundus, together with recognition that changes in the fundus arise in the wake of systemic disease, and may at times lag somewhat behind them, has reestablished a major role for the ophthalmoscopic picture. As a result, most clinical classifications of hypertension depend more on the appearance of the eyegrounds than on any other single criterion.

CLINICAL MATERIAL

The cases reported here cover an investigation that was begun several years ago, in cooperation with studies by Dr. Keith S. Grimson, now of Duke University, and Dr. Alf S. Alving, Dr. Wright Adams and others of the University of Chicago, to determine the relative values of subtotal and of total paravertebral sympathectomy in the treatment of hypertension. The operations of this series were done by Dr. Grimson and his associates at the Albert Merritt Billings Hospital, and the technic and surgical results have been separately

From the Division of Ophthalmology, Department of Surgery of the University of Chicago.

Read at a meeting of the Chicago Ophthalmological Society, March 15, 1943.

1. Goldblatt, H.; Lynch, J.; Hanzal, R. F., and Summerville, W. W.: Studies on Experimental Hypertension, J. Exper. Med. **59**:347, 1934. Goldblatt, H.: Studies on Experimental Hypertension, Am. J. Clin. Path. **10**:40, 1940.

2. Page, I. H.: A Method for Producing Persistent Hypertension by Cellophane, Science **89**:273, 1939.

3. Harrison, T. R.; Blalock, A., and Mason, M. F.: Effects on Blood Pressure of Injection of Kidney Extracts of Dogs with Renal Hypertension, Proc. Soc. Exper. Biol. & Med. **35**:38, 1936.

4. Page, I. H.: The Vasoconstrictor Action of Plasma from Hypertensive Patients and Dogs, J. Exper. Med. **72**:301, 1940. Page, I. H., and Helmer, O. M.: A Crystalline Pressor Substance (Angiotonin) Resulting from the Reaction Between Renin and Reninactivator, ibid. **71**:29, 1940.

5. Page, I. H.; Helmer, O. M.; Kohlstaedt, H. K.; Kempf, G. F.; Corcoran, A. C., and Taylor, R. D.: A Progress Report of Investigations Concerned with the Experimental Treatment of Hypertension with Kidney Extracts, Ann. Int. Med. **18**:29-41, 1943.

6. Heymans, C.: Some Aspects of Blood Pressure Regulation and Experimental Arterial Hypertension, Surgery **4**:487, 1938.

reported by him.[7] Other sympathectomies performed since the original series will not be considered here. The full operative procedure required two transthoracic and one transabdominal operation. The stellate ganglion and the entire thoracic sympathetic ganglionated chain, the splanchnic nerve and its branches, the major portion of the celiac ganglion and part, or all, of the lumbar sympathetic ganglionated chain were removed. In some cases the abdominal operation was omitted. In all the patients a typical Horner syndrome developed bilaterally, with varying degrees of ptosis and miosis, although enophthalmos was irregular and slight. In several there developed changes in reading tolerance sufficient to merit note, but, unfortunately, preoperative and postoperative studies of accommodation were not undertaken. Postoperative sweating tests contributed further proof of the absence of sympathetic function in the affected areas.

The observational routine before and after sympathectomy included determinations of the blood pressure every four hours under basal conditions, as well as after immersion of the hands in ice water and with the visual fields, refraction and such other studies as were deemed advisable.

The series contained 18 hypertensive patients, 10 of whom were males and 8 females. The ages ranged from 18 to 50 at the time of operation, with an average age of 35.8 years. Four patients were in Keith-Wagener [8] group I (mild hypertension); 4, in group II (moderate hypertension); 4, in group III (advanced hypertension), and 6, in group IV (very severe hypertension). Six patients had had cerebral hemorrhage with hemiplegia before operation, and 2 others had had severe episodes of hypertensive encephalopathy. There were 3 operative deaths in the series, 1 of a patient in Keith-Wagener group III and 2 of patients in group IV. Two deaths were due to sudden respiratory failure on the second and the fifth postoperative day respectively; the other death was the result of late pneumonia and uremia. Three other patients, tabulated as surviving operation, have died since. One lived for two and one-quarter years after the third stage of hypertension and died of cardiac failure, renal insufficiency and intestinal volvulus. Two others died at home, and

TABLE 1.—*Effect of Subtotal to Total Sympathectomy on Blood Pressure* *

Keith-Wagener Group	Age of Patient, Yr.	Preoperative Blood Pressure, Supine Position, O. P. D.†	Preoperative Blood Pressure, Supine Position, Hospital	Postoperative Blood Pressure, Supine Position, O. P. D.	Postoperative Blood Pressure, Supine Position, Hospital	Postoperative Blood Pressure, Standing, O. P. D.	Time in Months
I	25	190/116	166/100	130/ 84	108/ 70	120/ 70	24
I	38	210/138	180/120	126/128	174/108	162/120	22
I	32	200/126	170/118	110/ 75	120/ 80	70/ 50	7
I	27	180/108	180/110	152/100	140/ 94	90/ 60	5
II ‡	42	224/120	200/120	200/108	136/ 94	138/ 92	24
II ‡	40	196/120	180/116	170/104	138/ 88	122/ 90	18
II	18	204/140	190/130	128/ 74	126/ 86	114/ 76	17
II	25	180/126	160/118	120/ 72	116/ 76	116/ 70	7
III	40	264/136	220/122	246/138	200/114	180/100	21
III	33	240/150	228/138	260/150	200/142	196/120	20
III	44	220/124	170/120	196/122	160/100	122/ 90	15
IV ‡	50	278/148	220/130	234/130	172/102	152/118	21
IV ‡	42	238/154	202/132	240/140	210/134	180/130	0
IV	40	280/138	226/150	220/142	182/120	184/132	8
IV ‡	28	228/130	178/120	140/ 86	138/ 88	100/ 76	7

* After Grimson.[7b]
† O. P. D. indicates an average for several office readings.
‡ Cerebral accident before operation.

patient under profound hypnosis induced with sodium amytal. Renal studies undertaken by Dr. Alving, of the department of medicine of the University of Chicago, included a urea clearance test, the Addis-Shevky urine concentration test, the taking of intravenous pyelograms and determinations of inulin and diodrast clearances. Circulatory tests, made by Dr. Wright Adams, included a roentgenographic study of the chest, an electrocardiographic reading, determinations of the arm to tongue circulation time and the venous pressure, estimations of blood volume and vital capacity, determination of cardiac output and exercise tolerance tests. Neurologic and psychiatric evaluations were also obtained. Ophthalmologically, an attempt was made to photograph each fundus before and after operation and to describe each fundus in detail before operation, with comments later concerning any changes observed in the posterior course. These examinations were supplemented by examination of the no autopsy was performed. The rest have survived for periods of from one and a quarter to three years. There was definite symptomatic improvement. Table 1, from Grimson's recent review,[7b] shows the effect on the blood pressure. Adams, Alving and associates [9] issued a preliminary report covering only the first seven months after operation. They found no significant consistent change in insulin or diodrast clearance, urine concentration ability, venous pressure, arm to tongue circulation time or size of the heart, either in the patients who did or in those who did not obtain good reduction in blood pressure. None of the circulatory changes found account for the drop in blood pressure when it occurred. They concluded that it seemed probable that the drop in pressure that occurs after sympathectomy is due to decrease in peripheral resistance in a large vascular bed.

7. (*a*) Grimson, K. S. Total Thoracic and Partial to Total Lumbar Sympathectomy and Celiac Ganglionectomy in the Treatment of Hypertension, Ann. Surg. **114**:753, 1941; (*b*) The Surgical Treatment of Hypertension, Internat. Abstr. Surg. **75**:421-434, 1942; in Surg., Gynec. & Obst., November 1942.

8. Keith, N. M.; Wagener, H. P., and Barker, N. W.: Some Different Types of Essential Hypertension: Their Course and Prognosis, Am. J. M. Sc. **197**:332, 1939.

9. Adams, W.; Alving, A. S.; Sandiford, L.; Grimson, K. S., and Scott, C.: The Effect of Bilateral Paravertebral Sympathectomy on the Cardio-Renal System in Essential Hypertension, Am. J. Physiol. **133**: 190-191 (June) 1941.

PREREQUISITES FOR CLASSIFICATION

It was difficult to review cases from an ophthalmologic standpoint with the Keith-Wagener classification. While it is recognized that this classification is effective in evaluating the condition of the hypertensive patient as a whole, certain difficulties arise when it is used with reference to the eye. For example, groups I and II of Keith and Wagener frequently present such similar fundus pictures that they are well nigh indistinguishable on the basis of the eyes alone. Peet and associates [10] recognized this in 1940, when they proposed their own classification to assist them in their studies. Fishberg's [11] classification of hypertensive neuroretinopathy, arteriosclerotic retinopathy and choked disk was helpful, but permitted no designation of degree within each group. Nor did it allow cross classification of changes in the fundus that were both hypertensive and sclerotic. The classification of vascular fundus disease originated by Gifford and MacPherson [12] was found to be better suited to the ophthalmologic aspects of this study than any of the others, but, unfortunately, it was impossible with this classification to evaluate the sclerotic components of the fundus apart from the hypertensive components. Since in such a study as this it was of interest to classify separately the sclerotic, organic disease of the vessels and the functional, acute hypertensive component, a classification that permitted this was necessary.

To classify the fundus accurately there must be agreement on certain axiomatic principles. The interpretations of spasm, light reflex, preorganic constriction, organic constriction, irregularity of lumen and arteriovenous nicking are so basic as to demand early consideration: It is well recognized that it is the blood column, not the vessel, which is seen in the normal fundus.[13] This is due to the transparency of the wall of the normal vessel. Only at and near the disk, where the vessel wall is thicker and less transparent, is the wall itself visible, appearing as a grayish sheathing on the blood column. The light reflex on the vessel is a combination of the reflex from the vessel wall (mainly at the adventitia-media interface) and the reflex from the blood column.[14]

A consideration of the light reflex from the penholder in figure 1 *a* is illustrative. The width of the light reflex is proportional to the diameter of the reflecting surface; that is, wherever the penholder is wide, the reflex is wide; where the diameter narrows, the reflex narrows. The same relation holds true for the vessels of the fundus; large vessels have wide reflexes, and smaller ones have narrower reflexes. The principle is also true in another respect: Let figure 1 *b* represent a normal artery in cross section.

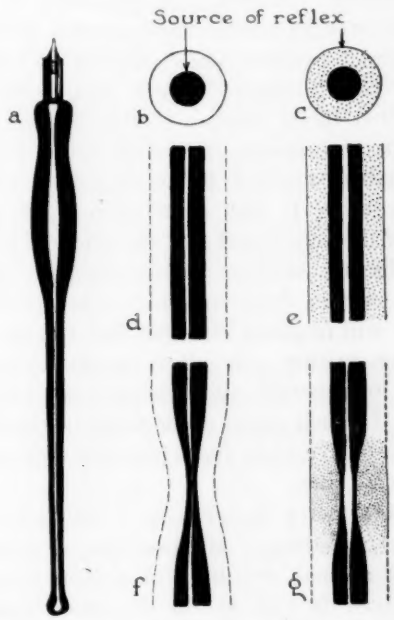

Fig. 1.—Variations in the light reflex (see text for details).

Although the arterial media is appreciable and contributes slightly to the reflex, the main source of the reflex is the surface of the blood column, seen ophthalmoscopically, as in figure 1 *d*. If the arterial media is thickened, hyalinized or made optically more dense by a sclerosing process, it takes on major importance as the source of the reflex, as shown in figure 1 *c*, and as seen ophthalmoscopically in figure 1 *e*. This principle is also applicable to a comparison of the normal vein and the normal artery. In the former the media is negligible, and all the reflex comes from the blood column, whereas in the latter there is sufficient media to produce some widening of the reflex. Thus, arteries normally

10. Peet, M. M.; Woods, W. W., and Braden, S.: The Surgical Treatment of Hypertension: Results in 350 Consecutive Cases Treated by Bilateral Supradiaphragmatic Splanchnicectomy and Lower Dorsal Sympathetic Ganglionectomy, J. A. M. A. **115**:1875-1885 (Nov. 30) 1940.

11. Fishberg, A. M.: Hypertension and Nephritis, ed. 4, Philadelphia, Lea & Febiger, 1939.

12. Gifford, S. R., and MacPherson, W. A.: A Classification of Vascular Fundus Diseases, Quart. Bull., Northwestern Univ. M. School **14**:65, 1940.

13. Duke-Elder, W. S.: Textbook of Ophthalmology, London, Henry Kimpton, 1940, vol. 3, p. 2677.

14. Wilmer, W. H.; Pierce, H. F., and Friedenwald, J. S.: The Light Streaks of the Retinal Blood Vessels, Arch. Ophth. **9**:368 (March) 1933.

have wider reflexes than veins of the same lumen diameter.

Figure 1 *f* represents an artery with a wall of normal transparency, physiologically stimulated to contract at a focal area. Since the vessel wall at the constricted area is transparent and the reflex arises mainly from the blood column, the narrowed blood column will give a narrower reflex. This phenomenon of narrowed blood column and narrowed light reflex is the expected picture of a true spasm, or preorganic constriction; indeed, it is the picture found in the early stages of hypertension and in cases of toxemia of pregnancy that arises without previous vascular disease. Figure 1 *g* represents a vessel with an area of considerable medial thickening and intimal proliferation, sufficient to encroach on the vessel lumen. If one judges from the constricted blood column alone, it differs little from the true spasm, shown in figure 1 *f*. But the notably widened reflex indicates that the blood column is not contributing the greater share of the reflex and that the thickened wall is the reflecting surface. Differentiation of preorganic spasm from organic sclerosis in this manner will facilitate classification in most cases, confusion arising only when spasm has existed over a long period and sclerosis has begun to appear. In such cases, other areas of the fundus in the same eye or in the fellow eye may provide the crucial clues.

Another factor in sclerosis is the appearance of vessel sheathing. Mention has already been made of normal sheathing of vessels about the disk, which is due to the increased thickness of the vessel and the greater optical density where the vessels originate. Sclerotic sheathing arises from loss of transparency of the vessel wall; it manifests itself as parallel white or yellowish white lines bordering the red blood column and should be seen at least 1 disk diameter away from the disk to be of significance. Frequently the sclerosis is insufficient to become visible in itself but may still alter the red character of the blood column to produce the familiar copper-red color, or when still more pronounced may, in combination with a wide reflex of increased brilliance, produce characteristic "silver wiring."

Arteriovenous compression and nicking were first described by Gunn,[15] in 1892. Although Gunn stated that "the appearance is interpreted as an evidence of high arterial tension," more recently Friedenwald[16] suggested:

> [Whereas these] cases usually present marked arterial hypertension. . . . , the constriction of the veins persists when, as the result of intercurrent disease or cardiac decompensation, the blood pressure falls to normal levels. The constriction is to be attributed, therefore, not to the hypertension directly, but to structural changes in the vessel wall.

Koyanagi's[17] observation of sclerotic changes, which convert the common adventitial sheath about the vein and artery at crossing sites into a constricting band, adds weight to this interpretation. Although venous thromboses at the sites of nicking are common, few authors have considered them of sufficient importance to merit a separate position in the classification of arteriosclerotic disease. But since nicking is understood to be a sclerotic phenomenon, and since severe nicking predisposes to venous occlusion at the site of the compression, such thromboses should be considered evidence of an extreme degree of sclerosis. One must tread this ground cautiously, for not all thromboses are the result of sclerotic compression, nor are all arterial closures sclerotic. But if one bars such irrelevant vascular disease as embolism and focal perivasculitis (tuberculous or otherwise) and causes other than arteriosclerotic-hypertensive disease, these focal vascular insufficiencies do indicate a most severe degree of sclerosis.

Finally come those factors of the fundus picture related not to sclerosis but to acute hypertensive "toxicity." The subtle changes of early disease have been best observed during acute hypertensive episodes without previous vascular disease, such as the toxemia of pregnancy.[18] The early development of edema of nerve fibers, which blurs the margins of the disk and frequently extends out into the retina above and below, has been widely noted, although the exact mechanism of the neurotoxicity has not been elucidated. That this is a reversible change has been repeatedly confirmed by observations of regression to the normal state after toxemia has ended. This type of neural edema is not to be confused with the frank papilledema seen in the late stages of malignant hypertension. In the latter condition the disk is measurably mushroomed forward, and there is increased intracranial pressure, whereas in the former the disk

15. Gunn, R. M.: Ophthalmoscopic Evidence of (1) Arterial Changes Associated with Chronic Renal Disease, and (2) of Increased Arterial Tension, Tr. Ophth. Soc. U. Kingdom **12**:124, 1892.

16. Friedenwald, H.: The Doyne Memorial Lecture: Pathological Changes in the Retinal Blood Vessels in Arteriosclerosis and Hypertension, Tr. Ophth. Soc. U. Kingdom **50**:452, 1930.

17. Koyanagi, Y.: Die Bedeutung der Gefässkreuzung für die Entstehung der Astthrombose der retinalen Zentralvene, Klin. Monatsbl. f. Augenh. **80**:219, 1928.

18. Dieckmann, W. J.: The Toxemias of Pregnancy, St. Louis, C. V. Mosby Company, 1941, chap. 8.

is flat, though fuzzy and wet, and the intracranial pressure is unaltered. Preorganic arterial spasm, another early sign that may parallel neural edema, has been discussed from its anatomic and ophthalmoscopic standpoint. Although the cause is obscure, it has been seen that spasms may relax and disappear,[19] or when they persist for a long time, they may go on to hyaline degeneration and sclerosis.

Although neural edema and spasm are early phenomena, this cannot be said about the flame-shaped hemorrhages and soft exudates seen in cases of hypertensive disease. With toxemia of pregnancy they are seen at a much later stage and must be interpreted as a beginning breakdown in the integrity of the vessel, sufficient to allow escape of fluid and formed elements of the blood. The form which the lesions take and their course and outcome are modified by degenerative changes and by invasion of phagocytes.

The superimposition of choked disk, with true elevation of the nerve head, is generally considered the final, most severe, stage, i. e., malignant hypertension. The papilledema arises not by local vascular processes, as in the case of neural edema, hemorrhage and exudate, but in the fashion of the papilledema of cerebral tumor, from increased intracranial pressure.

CLASSIFICATION

With these factors in mind, the classification in table 2 was devised. The arteriosclerotic and the acute factors are evaluated separately and classified as of four grades, according to the following criteria: If there is beginning disease of the vessel, such as slightly widened reflex, early crossing signs or sheathing or irregularity of the lumen, the condition is designated as grade A_1. Patients with this stage of the disease may have slight derangement of pigment at the macula but no visual defect. If there is advanced vascular disease, with notable widening of the reflex stripe or severe arteriovenous deviation or nicking, the condition is classified as grade A_2. At this stage there may be hard, shiny exudates. If, in addition to changes characteristic of grade A_2 there are signs of a focal vascular insufficiency, such as venous thrombosis, or other vascular occlusions, the designation is grade A_3. An old thrombosis may show a field defect only. Perhaps certain other conditions, such as macular lesions on a vascular basis, may actually belong to this type, but for the present they are excluded from consideration. Absence of any organic changes places such a fundus in the A_0, or normal group. The hypertensive classifications are straightforward. Focal arteriolar spasm or mild edema of the nerve fibers of the disk or retina is classified as grade H_1. Hemorrhages or soft exudates are classified as grade H_2. If papilledema has supervened, the designation is grade H_3.[20] Again, absence of any acute signs places such a fundus in the H_0, or normal, group. Each patient is classified according to both the A and the H groupings. Thus, a patient's classification may be H_1 and yet A_3 or A_1 and H_3. In this fashion, a separate evaluation is made of organic vascular sclerosis and preorganic acute toxicity.

TABLE 2.—*Classification of Vascular Disease of the Fundus*

A_0H_0—Normal	
A_1: Mild arteriolar sclerosis	H_1: Arteriolar constriction
A_2: Severe arteriolar sclerosis	H_2: Hypertensive retinopathy
A_3: Severe arteriolar sclerosis with focal insufficiency	H_3: Hypertensive retinopathy with papilledema

RESULTS OF SYMPATHECTOMY

Table 3 summarizes the changes in the fundus in each of the patients and, at the same time, gives some of the pertinent clinical information. The designations for postoperative blood pressure that appear in the table constitute a code which facilitates tabulation. The blood pressure readings published by Grimson have been

19. Haselhorst, G., and Mylius, K.: Zur Frage der Gefässkrampfe bei Eklampsie, Zentralbl. f. Gynäk. **52**: 1180, 1928.

20. Alving, in a personal communication, suggested that the purpose of classification would be better served if H_3 were removed from the H series since papilledema is etiologically different from the other acute signs. He suggested that papilledema be made a third, and separate, factor, as it is in Fishberg's classification. This led to the temporary adoption of a third designation P (for papilledema), with the fundi classified according to the three factors A, H and P. The diopters of papilledema were expressed in the P subscript, so that $A_1H_2P_2$ might represent a fundus of mild sclerotic changes with hemorrhages or soft exudates and 2 D. of papilledema. However, in many cases of papilledema it is difficult to assess whether hemorrhages and exudates are primarily hypertensive or actually secondary to the choked disk. Also, papilledema produces secondary arterial constriction and venous dilatation, which further confuse the picture. Altogether, papilledema makes evaluation of the other factors so difficult that it is questionable whether separation of a P factor provides greater accuracy. For the sake of simplicity it would seem that papilledema can still be represented in the H series if the difference in pathogenesis of hypertensive hemorrhages and exudates and that of choked disk is kept in mind. Only in cases in which choked disk occurs with vessel spasms and without hemorrhage or exudate would classification be difficult, and such an occurrence is not common.

arranged into four groups. I signifies that the postoperative blood pressure was less than 140 systolic and 90 diastolic when the patient was in both the supine and the standing position; II signifies that the blood pressure was less than 140 systolic and 90 diastolic with the patient in the standing position but that it continued to be elevated with the patient lying down. III indicates that the blood pressure was appreciably lower after than before operation, but not down to 140 systolic and 90 diastolic, and IV, that the blood pressure was essentially unchanged by operation.

TABLE 3.—*Appearance of the Fundus in Hypertensive Patients After Sympathectomy*

	Age	Sex	Keith-Wagener Classification	Fundus Picture: Preoperative	Fundus Picture: Postoperative	Postoperative Blood pressure *
R. B.	25	F	I	A_1H_1	A_1H_0	I
I. M.	38	F	I	A_1H_1	A_1H_1	IV
H. M.	31	F	I	A_1H_1	A_1H_1	I
C. C.†	27	M	I	A_0H_1	A_1H_1	II
H. S.	42	M	II ‡	A_1H_2	A_1H_1	III
E. R.	39	M	II ‡	A_1H_1	A_1H_1	I
J. W.	18	F	II	A_0H_1	A_1H_0	I
J. L.	25	F	II	A_0H_1	A_1H_1	I
L. M.	40	F	III	A_3H_2	A_3H_1	III
A. W.	32	F	III	A_2H_2	A_2H_1	IV §
Mc. T.	44	M	III	A_1H_2	A_1H_1	II ‖
G. H.	43	M	III	A_3H_1	Died	
L. M.	50	M	IV ‡	A_2H_2	A_2H_1	III
D. Mc.	42	M	IV ‡	A_2H_3	A_2H_1	IV ‖
P. L.	40	M	IV	A_1H_3	A_1H_1	III
V. M.	28	M	IV ‡	A_1H_3	A_1H_1	I
R. E.	48	M	IV	A_2H_3	Died	
C. D.	32	F	IV ‡	A_3H_3	Died	

* I indicates a blood pressure of less than 140 systolic and 90 diastolic when the patient was in the supine and standing positions; II, a pressure of less than 140 systolic and 90 diastolic when the subject was standing but an elevation of pressure in the supine position; III, a pressure lower than before operation, but not down to 140 systolic and 90 diastolic, and IV, no lowering of blood pressure.

† The patient had polycythaemia vera.

‡ A cerebral hemorrhage occurred before operation.

§ The patient died two and a half years after operation.

‖ The patient died at home in the follow-up period. No autopsy was performed.

The cases of certain of the patients were sufficiently representative that they merit individual presentation.

R. B., a housewife, was 25 at the time of her operation. She was found to have a blood pressure of 180 systolic and 110 diastolic, with blood and albumin in her urine, during a pregnancy three and one-half years before operation. After a therapeutic abortion her blood pressure rose to 220 systolic and 120 diastolic. While she was under medical management for about two and one-half years, the blood pressure remained about 180 systolic and 110 diastolic. The urine was normal. The fundus showed changes characteristic of grade A_1H_1; that is, there were mild sclerotic vascular changes, as well as some spasms. After sympathectomy there was a prompt drop of the blood pressure to and below normal levels. This patient has now been followed over two and one-half years, and on the last admission to the hospital her blood pressure averaged 110 systolic and 65 diastolic. Figure 2 shows the picture of the fundus at the last admission. The old areas of arteriolar sclerosis are in bold contrast to the more normal vasculature in other areas of the fundus. No spasms are visible at present.

Fig. 2.—R. B., aged 25 at the time of operation, had had persistently normal blood pressure since operation. The mild degree of focal arteriolar sclerosis (widening of the arteriolar light reflex with narrowing of the lumen of the vessel) is readily noted.

Equally good results were obtained in the case of V. M., a laborer aged 28, who was first seen seven weeks after a paralytic stroke. Examination showed a blood pressure of 230 systolic and 150 diastolic and

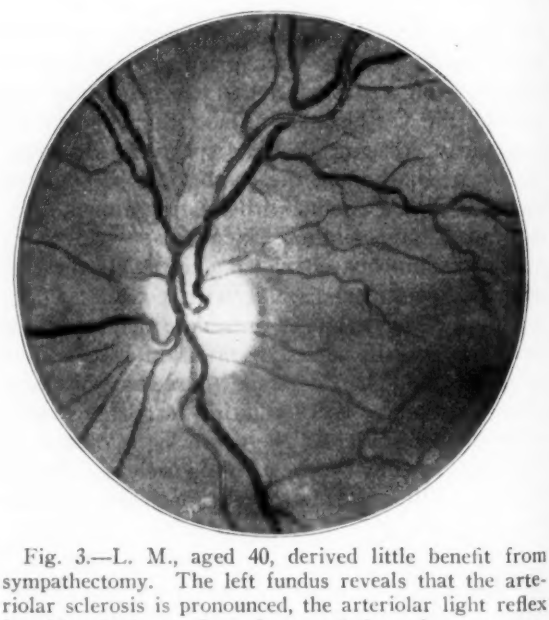

Fig. 3.—L. M., aged 40, derived little benefit from sympathectomy. The left fundus reveals that the arteriolar sclerosis is pronounced, the arteriolar light reflex is widened almost throughout and the veins are practically cut into "sausages" by severe nicking. Examination of the right eye showed a field defect due to an old venous thrombosis, and punctate exudate, such as are seen with old thromboses of branch veins in this region of the fundus.

right hemiplegia. The fundus showed some edema of the disk, with edema streaking out into the retina, mild crossing signs and a fresh cotton wool exudate. While the patient was under observation, the edema of the nerve head increased to frank papilledema, and sympathectomy was performed. The blood pressure has been consistently normal with the patient in both the standing and the recumbent position for the past year and a half since operation. Papilledema and exudate have disappeared, although some residual edema of the nerve fibers on the disk remains.

One often learns considerably more from the failures with a procedure than from the successes: The preoperative blood pressure curve in the case of L. M., a 40 year old widow, was about 236 systolic and 128 diastolic. Medical management over the course of a year and eight months produced no beneficial effect. The result of operation also left much to be desired, although there was some initial drop in the blood pressure (180 systolic and 100 diastolic in the recumbent position and 200 systolic and 114 diastolic in the supine position), and the patient claimed she felt better. Figure 3 shows the preoperative appearance of the fundus in the patient. The degree of the organic vascular component was pronounced, although papilledema was absent.

One of the fatalities was G. H., aged 43. He had macular degeneration in the right eye, possibly on a vascular basis, and thrombosis of a branch vein in the left eye. In the fundus the crossing signs were pronounced, the arteriolar sclerosis was severe, and hemorrhages were seen in the area of the venous thrombosis.

Table 4 shows the distribution of fundus groupings before and after operation. The arteriolar sclerosis showed a slight tendency to shift toward the higher grades. In the 3 patients with grade A_0 who showed no sclerosis at first, grade A_1 changes developed. A patient who had grade A_2 signs shifted to grade A_3 signs. Two patients with grade A_2 changes and 1 with grade A_3 changes died. It is difficult to assess such an increase in sclerosis as was observed. The findings in the H series are in direct contrast to those of the A series. After sympathectomy there was a definite shift to the more benign grades of hypertensive disease, the shift occurring in 10 patients. All the papilledema disappeared in the patients who survived (2 patients with papilledema died after operation). In all the patients with grade H_2 changes hemorrhage and exudate were absorbed, the picture shifting to grade H_1. It appears significant that all hypertensive changes did not disappear entirely. In 13 of the 15 patients who survived, evidence of spasm remained, as well as some edema of nerve fibers, even though the disk was not measurably elevated.

In table 5 the fundus picture correlated with the postoperative blood pressures. There is a notable correlation between the degree of sclerosis and the prognosis of the patient in so far as both the drop in blood pressure and the outlook for survival are concerned. The patients with the least sclerosis achieved normal blood pressures, while those with the most severe sclerosis obtained the least decrease in blood pressure. It was also found that the mortality was limited exclusively to the patients with the greatest degree of sclerosis. Whereas there was a high degree of correlation in the A series, the H series presented a somewhat different pic-

TABLE 4.—*Distribution of Fundus Types*

Classification of Fundus	Number of Patients	
	Preoperative	Postoperative
A_0	3	0
A_1	8	11
A_2	6 (2 died)	3
A_3	1 (1 died)	1
	18 (3 died)	15
H_0	0	2
H_1	8 (1 died)	13
H_2	5	0
H_3	5 (2 died)	0
	18 (3 died)	15

TABLE 5.—*Relation of Fundus Picture to Effect of Sympathectomy on Blood Pressure and Mortality Rate*

Classification of Fundus	Effect on Blood Pressure *				Number of Deaths
	I	II	III	IV	
A_0	1	1	..	..	..
A_1	4	1	2	1	..
A_2	..	..	2	2	2
A_3	..	..	..	..	1
H_0	..	..	..	..	..
H_1	5	1	..	1	1
H_2	..	1	3	1	..
H_3	1	..	1	1	2

* The grading of blood pressure is the same as that in table 2.

TABLE 6.—*Relation of Fundus Picture to Decrease in Diastolic Pressure and Mortality Rate*

Classification of Fundus	Diastolic Pressure Decrease, Mm.					Increase	Deaths
	40-49	30-39	20-29	10-19	0-9		
A_0	2	..	..	1	..	..	..
A_1	..	3	4	1	..	..	..
A_2	..	..	1	..	1	2	2
A_3	..	..	..	..	..	..	1
H_0	..	..	..	..	..	..	..
H_1	2	2	1	2	..	..	1
H_2	..	..	3	..	1	1	..
H_3	..	2	..	..	..	1	2

ture. Although a general trend suggests a better prognosis for patients with the least morbid changes, there is more scatter than in the A series, and the correlation appears to be less rigid. Correlation of the fundus picture with the numerical drop in diastolic blood pressure (table 6) rather than arbitrary grouping reveals the same tendencies, although not to such a striking degree. Patients with the lesser degrees of sclerosis, again, showed a more consistent

drop in diastolic pressure, and those with greater degrees of sclerosis showed the least fall in diastolic pressure. In the H series, the same trend is suggested, but the scatter is greater and the correlation less valid. In table 7 the age of the patient is correlated with the postoperative blood pressure. Despite considerable scatter, there is the suggestion that the best results occur in the youngest patients and the poorest results in the oldest patients.

COMMENT

The study has revealed certain trends, and, within the limits of error that are imposed by the small series, it is justifiable to make certain observations. First, coincident with a fall in the systolic and diastolic blood pressures in many cases, the acute signs in the fundus disappeared after sympathectomy. Papilledema, hemorrhages and exudates were all noted to disappear, although it is significant that some residual edema of nerve fibers about the disk and some vessel spasms persisted in a large majority of patients. Thus, the eyegrounds tend to confirm the beneficial effects that have been found to follow sympathectomy.

TABLE 7.—*Relation of Age to Effects on Blood Pressure and Mortality Rate*

Age	Effect on Blood Pressure *				Died
	I	II	III	IV	
25	3	..	..	..	..
26-30	1	1	..	..	..
31-35	1	..	..	1	1
36-40	1	..	1	1	..
41-45	..	1	1	1	1
46-50	..	..	1	..	1

* The grading of blood pressures is the same as that in table 2.

The persistence of some degree of signs of "toxic hypertension" in the fundus, such as spasm and neural edema, even after sympathectomy, which denervates the sympathetic supply to the ocular vessels, must be regarded as highly significant. In cases of toxemia of pregnancy in which such signs are noted, they start to disappear almost immediately after delivery of the baby, and in the course of several days (rarely more than a few weeks) they are completely gone. If the neural edema and spasm that persisted in the large majority of the patients are indicative of continuing vascular disease, as indeed they appear to be, one would be forced to the conclusion that sympathectomy has not completely arrested the disease process, even though it has provided relief in many instances from the elevated blood pressure.

Another impression that appears justifiable concerns the prognostic value of the fundus picture. Heretofore, the prognosis for a patient has always been measured in terms of the acute hypertensive signs, namely, hemorrhage, exudate and papilledema, possibly because these signs were the most easily and unmistakably noted. The prognostic value of these signs has led to their being used as a basis of classification practically universally. From this study, however, it appears that the acute hypertensive signs are actually of less prognostic value than the sclerotic signs, in so far as benefit from operation is concerned. This is not at all startling, since the acute hypertensive signs are all reversible and may disappear without trace, whereas the degree of sclerosis is for the most part irreversible. Further evidence in this regard arises from a consideration of the main theories that have been suggested concerning the mechanism of sympathectomy. Crile [21] suggested that denervation of the adrenal medulla was a major factor. Other authors have at various times suggested that the effect was produced by such factors as dilation of renal vessels, dilation of the cardiac vessel bed and dilation of the splanchnic bed. Except for the neurologic concept of Crile, all the other theories depend on the ability of an arterial bed to dilate. Rigidity of this bed, i. e., sclerosis, would be an insurmountable obstacle to dilation and should be the main limiting factor in the achievement of a good result. Page and associates reported that patients suffering from the malignant syndrome showed reversal of the morbid changes in the eyegrounds after administration of renal extract.[5] But his published clinical charts show that the morbid changes which regressed were the hemorrhages, papilledema and exudates, while the sclerotic changes in the vessels appeared to remain fixed, or even progressed. It would be interesting to learn whether the degree of sclerosis has any relation to the success or failure of administration of renal extract.

If, then, the degree of sclerosis is the basic factor in evaluating prognosis with respect to surgical treatment, any factor that affects the degree of sclerosis should secondarily be of prognostic value. It is possibly for this reason that age is of prognostic value, since in younger persons sclerosis has not had sufficient time to develop. Or, perhaps, duration of the disease, if it could be accurately known, might have the same prognostic value, since it will affect the degree of sclerosis. Finally, perhaps the degree of the acute hypertensive component, which is still emphasized so greatly, is really of value only in so far as it affects the organic sclerosis.

21. Crile, G.: The Surgical Treatment of Hypertension, Philadelphia, W. B. Saunders Company, 1938.

These suggestions are in keeping with the statement of Woods and Peet [22] that a favorable prognosis seems to depend on the degree of retinal arteriolar sclerosis rather than on the level of the blood pressure, the absence of retinitis with hemorrhage and exudate or papilledema. This well emphasizes the need for a classification that will give the proper evaluation to the arteriolar sclerosis. Such a classification, tentative though it may be, has been suggested. Experience may dictate further revision in this respect.

SUMMARY

Eighteen patients of all ages, and with all stages of hypertension, were subjected to total or subtotal paravertebral sympathectomy of the most extensive type yet reported, and of particular note in that the retinal vessels were also denervated by stellate ganglionectomy. In the 15 patients who survived operation, varying degrees of lowering of blood pressure were obtained. In order to secure separate evaluation of arteriolar sclerosis and the acute hypertensive changes in the fundi, a double classification was devised. In the arteriosclerotic division, A_0 represented no sclerotic changes in the fundi. Minimum arteriolar sclerotic signs, such as widened arterial reflex, irregularity of lumen and early crossing signs, were designated as grade A_1. Advanced vascular disease, with pronounced widening of the reflex stripe and notable nicking, was termed grade A_2. Evidence of focal vascular insufficiency, such as venous thrombosis or arterial closure, superimposed on changes of the A_2 type, was graded as A_3. The acute hypertensive signs were evaluated separately: Absence of any acute hypertensive phenomena was diagnosed as H_0; presence of edema in the nerve fibers, blurring of the disk or preorganic vessel spasm, as H_4; hemorrhage or soft exudates, as H_2, and papilloma with measurable elevation, as H_3. All patients received both A and H designations; e. g., A_1H_2 might represent a fundus of early sclerosis with hemorrhage, exudate and vasospasm.

The studies of the fundi tended to confirm the beneficial effects of sympathectomy, since hemorrhages, exudates and papilledema disappeared; but it was significant that acute signs, such as vessel spasm and neural edema, persisted in a large majority of patients despite sympathetic denervation of the vessels of the eye. The degree of arteriolar sclerosis appeared to be of greater prognostic value than other retinal signs in evaluating the decrease in blood pressure to be expected after operation. Patients with the least retinal arteriolar sclerosis showed the best results after sympathectomy. This has emphasized the need for classification that provides adequate evaluation of the arteriosclerotic, as well as the acute, hypertensive phenomena.

22. Woods, W. W., and Peet, M. M.: The Surgical Treatment of Hypertension: II. Comparison of Mortality Following Operation with that of Wagener-Keith Medically Treated Control Cases, J. A. M. A. **117**: 1508-1515 (Nov. 1) 1941.

THE CORNEA

VII. PERMEABILITY TO WEAK ELECTROLYTES

DAVID G. COGAN, M.D., AND ERWIN O. HIRSCH, B.A.
BOSTON

Penetration of dissolved material through the cornea is believed to be a function primarily of phase solubility. The epithelium and the endothelium of the cornea are barriers to substances that are not soluble in fats, while the stroma similarly is a barrier to substances not soluble in water. Weak electrolytes require special consideration not only because they include the important group of alkaloids used clinically but because their solubilities in fat and water vary according to their degree of dissociation. In the present paper, studies will be reported on the effect of variations in this dissociation on the penetration of weak electrolytes through the cornea.

Within a range that is characteristic for each substance, weak bases become progressively dissociated with low hydrogen ion concentrations and weak acids with high hydrogen ion concentrations. In the undissociated form (free base) most weak organic electrolytes are fat soluble and variously water soluble, while in the dissociated form (salts) all are water soluble and most are nonfat soluble.

The substances used in studying the effect of dissociation on permeability through the cornea were selected on the basis of freedom from toxic effects, variation in dissociation over an appropriate range of hydrogen ion concentrations and adaptability to quantitative measurement. The weak base aniline and the weak acid salicylic acid were the two electrolytes most thoroughly studied. The degrees of dissociation of aniline and salicylic acid at different hydrogen ion concentrations were determined from the Henderson-Hasselbalch equation, using the dissociation constants of 4.6×10^{-10} and 1.06×10^{-3} respectively.

THE EXCISED CORNEA

The method employed for measuring permeability of the excised cornea was essentially the same as that previously described.[1] Corneas, with and without epithelium, were attached to the ends of tubes, and the amount of test substance transferred from the tube into the flask was determined at the end of an arbitrary period of time. The period varied for the different test substances but was always considerably less than that necessary for equilibrium.

The volume of the fluid in the tube was 1 cc. in all cases. The concentration of the test substance selected varied with the aqueous solubility of the free base. The fluid in the tube was buffered by the addition to the test solution of two-tenths–molar citric acid or tenth–molar sodium phosphate or suitable mixtures of the two substances. In all cases the fluid in the tube was hypertonic to that in the flask.

The volume of the fluid in the flask was 5 cc. and in most of the experiments it was not buffered. So long as the epithelium was present, the hydrogen ion concentration of the fluid in the flask did not vary more than 0.6 p_H unit despite the use of fluids in the tubes with p_H values ranging from 3 to 10.5. In the absence of the epithelium, however, the p_H of the flask fluid approximated that of the tube fluid in the course of the experiments.

The hydrogen ion concentration was determined electrometrically for all solutions prior to the experiments and for representative samples of fluid from the tube and from the flask after the experiments.

The major experiments were run in sextuplicate, the average deviation from the mean being ± 10 per cent.

On the conclusion of each experiment the integrity of the epithelium or the completeness of its removal was checked by transfer of fluorescein.

The amount of aniline transferred was determined photoelectrically by the standard calcium hypochlorite method.[2] Neither the buffer nor the corneal eluate produced any interference. The transfer of salicylic acid was determined photoelectrically, also, by the ferric chloride method. Inasmuch as proteins and salts were found to interfere with the test, the standard colorimetric curve was obtained by adding known amounts of salicylic acid to eluate blanks. Within the range tested both substances obeyed Beer's law, and an accuracy of ± 5 per cent was attained.

Since the appropriate degrees of dissociation were attained by varying the hydrogen ion concentration of the tube fluid, it was first necessary to establish what range of hydrogen ion concentrations would be tolerated by the epithelium. This was determined by taking advantage of the fact previously observed that the epithelium was an effective barrier to sodium chloride so long as it was intact. A series of tubes holding epithelium-stroma combination were partly filled with a 5 per cent solution of sodium chloride buffered with a phosphate–citrate mixture over a wide range of hydrogen ion concentrations. The transfer of chlorides was measured after eighteen hours. The epithelium

From the Howe Laboratory of Ophthalmology, Harvard Medical School.

1. Cogan, D. G.; Hirsch, E. O., and Kinsey, V. E.: The Cornea: VI. Permeability Characteristics of the Excised Cornea, Arch. Ophth. **31**:408 (May) 1944.

2. Snell, F. D., and Snell, C. T.: Colorimetric Methods of Analysis, New York, D. Van Nostrand Company, Inc., 1937, vol. 2, pp. 408-410.

maintained its normal barrier properties during the eighteen hours of the experiment with variations in the p_H of 3.5 to 10.2. Below and above this range the transfer of chlorides was abnormally increased, and the epithelium was assumed to be damaged.

1, together with the theoretic association curve for aniline. The duration of the experiment was six hours. The greatest amount of aniline transferred was arbitrarily plotted to correspond on

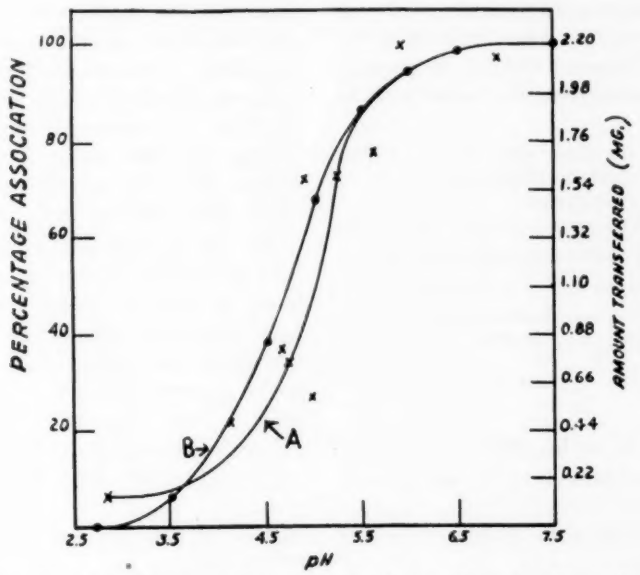

Fig. 1.—*A*, average amount of aniline transferred in six hours through the excised cornea from solutions of various hydrogen ion concentrations (phosphate-citrate buffer). *B*, association of aniline at various hydrogen ion concentrations, determined with the Henderson-Hasselbalch equation.

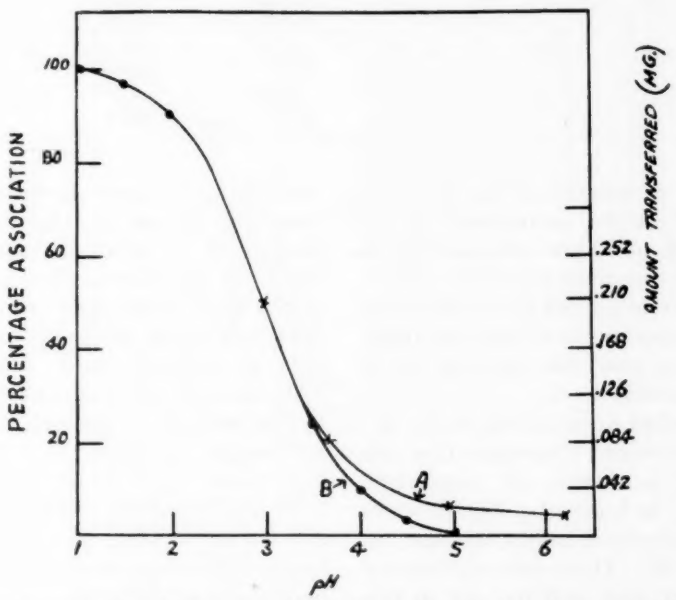

Fig. 2.—*A*, average amount of salicylate transferred in two hours through the excised cornea from solutions of various hydrogen ion concentrations (phosphate-citrate buffer). *B*, association of salicylate at various hydrogen ion concentrations, determined with the Henderson-Hasselbalch equation.

The results obtained for the permeability of aniline through the cornea at various values for the p_H within a range compatible with the integrity of the epithelium are presented in figure

the scale to 100 per cent "association." It will be seen that aniline was transferred across the epithelium-stroma combination according to the amount of undissociated aniline in the test fluid.

When stroma only was used, the amount transferred in the test period was approximately the same for all hydrogen ion concentrations.

The permeability of the epithelium-stroma combination of the cornea to salicylic acid was similarly plotted in figure 2, together with the theoretic association curve. The duration of the experiment was two hours. Owing to damage to the epithelium, measurements could not be made at ranges in the p_H of less than 3, and here only 50 per cent of the salicylic acid was associated. The amount transferred at this hydrogen ion concentration, therefore, corresponds on the ordinate of the graph to 50 per cent association. Again it will be seen that there is a close correlation between the association and the permeability curve. In parallel experiments the amount transferred through stroma only was constant for all hydrogen ion concentrations.

TABLE 1.—*Solubility of the Base and Salt of Aniline and of Salicylic Acid in Water and in Fat (Tributyrin)*

Test Substance	Solubility, Gm. per 100 Cc. Solvent	
	Water	Fat (Tributyrin)
Aniline	3.8	Miscible in all proportions
Aniline hydrochloride	107	Less than 0.017
Salicylic acid	0.20	8.2
Sodium salicylate	110	Less than 0.017

To determine whether or not these results are consistent with our previous conclusion that corneal permeability is a function of phase solubility, it is necessary to know the solubilities of dissociated and undissociated aniline and salicylic acid in water and in fat. These were determined by dissolving the free base and the salt in distilled water and in fat (tributyrin) at room temperature. It is assumed that the solvent properties of the fat in the corneal epithelium are not greatly different from those in the more available tributyrin. The results, recorded in table 1, indicate that the free bases of aniline and salicylic acid are similar to other substances which penetrate the epithelium-stroma combination in being appreciably soluble in fats, while the salts, which penetrate poorly, have little fat solubility. Both are soluble in water.

For purposes of comparison, the permeability through excised conjunctiva and sclera was determined for aniline at different hydrogen ion concentrations according to a technic previously described. The results were qualitatively similar to those obtained for the cornea; the conjunctiva acted as a considerable barrier to the transfer of aniline salt but not to aniline base, while the sclera, like the corneal stroma, was relatively freely permeable to both salt and base.

So far as the results with aniline and salicylic acid hold in general for other weak electrolytes, it may be anticipated that weak organic bases penetrate the cornea best at relatively high hydrogen ion concentrations and weak organic acids at relatively low hydrogen ion concentrations. The range over which this variation in the hydrogen ion concentration is effective varies according to the dissociation constant for each electrolyte, or, more specifically, with the corresponding changes in solubility. From the practical point of view, the most important weak bases are the various alkaloids and the majority of the local anesthetics, while among the more important weak acids are such metabolic products as carbonic acid, lactic acid, β-hydroxybutyric acid and pyruvic acid.

TABLE 2.—*Penetration Through the Cornea of Several Alkaloids in Solutions Buffered at Different Hydrogen Ion Concentrations*

	p_H at Which There is 50% Dissociation	Initial Concentration in Tube, %	Duration of Experiment, Hr.	Percentage of Total Test Substance Transferred		Analytic Test
Atropine	9.15	0.2	1½	<0.25 at p_H 4.3	2.75 at p_H 9.0	Pulewka, P.: Arch. f. exper. Path. u. Pharmakol. **168**: 307-318, 1932
Ephedrine	9.40	5.0	19	4.0 at p_H 5.3	16.7 at p_H 10.1	Chen, K. K.: J. Am. Pharm. A. **18**: 110-116, 1929
Pilocarpine	7.40	5.0	16	0.4 at p_H 4.5	2.2 at p_H 7.8	The Merck Index,[9] test 1759

The penetration through the cornea was tested for several common alkaloids, solutions being used which represented two degrees of dissociation, i. e., solutions buffered at different hydrogen ion concentrations. The range of hydrogen ion concentrations over which dissociation occurs is, of course, different for each alkaloid. The hydrogen ion concentration at which 50 per cent dissociation occurs was determined for each alkaloid by electrometric titration, and, as far as possible, permeability tests were made with solutions buffered above and below this value.

Certain difficulties were encountered in measuring corneal permeability to alkaloids which were not previously experienced to any

great extent with aniline. Most important was the instability of the alkaloids, especially in alkaline solutions. It was found, however, that, of the three alkaloids used, atropine showed no significant decomposition for two hours, while ephedrine and pilocarpine were stable for at least twenty hours. These periods were all longer than those used in the experiments.

The results of testing the corneal permeability to atropine, ephedrine and pilocarpine, together with other pertinent data, are presented in table 2. In all cases transfer was greater in the more alkaline mediums, that is, in solutions in which the alkaloid was present t[illegible] greater extent in the form of the free base.

The results accord with those Swan and White [3] obtained for penetration of procaine into the cornea at different hydrogen ion concentrations and with the observations of Fosdick, Hansen and Dragstedt [4]; Regnier,[5] and Gerlough [6] on the duration of corneal anesthesia with variations in the hydrogen ion concentration of a number of local anesthetics. The results further indicate that the selectivity of corneal permeability, or more especially, of the epithelium, is similar to that which has so abundantly been demonstrated for the individual cell, since Overton [7] first showed that free bases penetrate the cell wall more readily than the salts.

THE CORNEA IN SITU

For studies on the intact cornea it was first essential to have a method by which the solution could be kept in contact with the living cornea for any desired time, and since the permeability of the cornea exclusively was being tested, it was essential that the solution should not come in contact with the conjunctiva. The customary procedure of placing an eye cup on the cornea and sealing its edges with petrolatum failed to secure a water-tight chamber. Pressure of the cup against the cornea was also unsatisfactory not only because of the technical inconveniences but because the procedure caused undesirable vascular congestion.

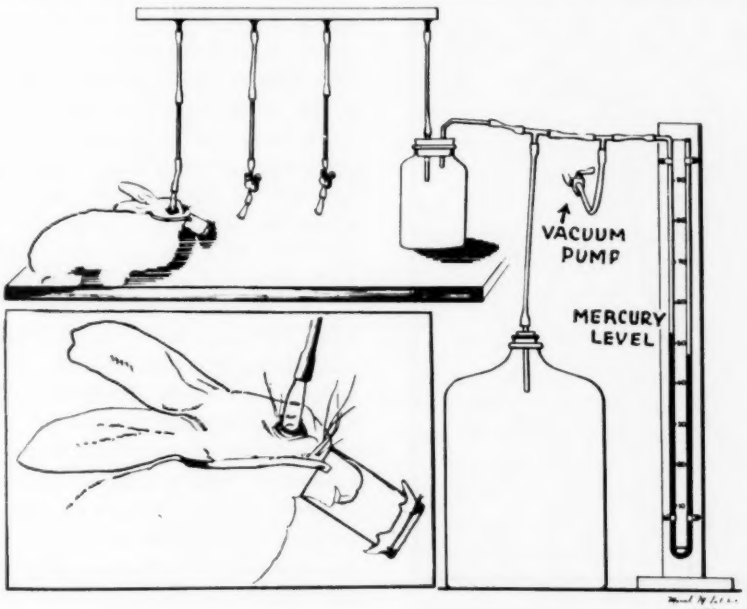

Fig. 3.—Apparatus employed for holding the eye cup in contact with the cornea in in vivo experiments. The test solution was injected through the rubber tubing at the top of the cup by means of a hypodermic needle after the negative pressure had been applied.

A method satisfactory for our purposes was obtained by the use of suction. A tube open at one end, with

3. Swan, K. C., and White, N. G.: Corneal Permeability: I. Factors Affecting Penetration of Drugs into the Cornea, Am. J. Ophth. **25**:1043, 1942.

4. Fosdick, L. S.; Hansen, H. L., and Dragstedt, C. A.: The Variation of Anesthetic Efficiency of Procaine Hydrochloride and Procaine Borate with p_H, Proc. Soc. Exper. Biol. & Med. **27**:529, 1923.

5. Régnier, J.: De l'augmentation des anesthésies produites sur la cornée par alcalinisation des solutions de chlorhydrate de cocaine, Compt. rend. Soc. de biol. **92**:605, 1925.

6. Gerlough, J. D.: The Influence of p_H on the Activity of Certain Local Anesthetics as Measured by the Rabbit's Cornea Method, J. Pharmacol. & Exper. Therap. **41**:306, 1931.

7. Overton, E.: Ueber die osmotischen Eigenschaften der Zelle in ihrer Bedeutung für die Toxikologie und Pharmakologie, Vrtljschr. d. naturf. Gesellsch. in Zurich. **41**:383, 1896; Ueber die allgemeinen osmotischen Eigenschaften der Zelle, ihre vermutlichen Ursachen und ihre Bedeutung für die Physiologie, ibid. **44**:88, 1899.

an orifice of 0.8 sq. cm. (less than the area of a rabbit's cornea), and tapered at the other end was connected with a closed system adjusted to maintain reduced pressure (fig. 3). The negative pressure employed was usually 60 mm. of mercury, but use of a negative pressure of 300 mm. for periods longer than those used in the experiments did not produce any apparent damage to the cornea. The test solution was injected into the tube through the rubber connecting piece at the top of the tube. The amount of test solution was usually 1 cc., but the quantity was not considered critical for the short interval experiments so long as the cornea was adequately covered. The hydrogen ion concentration of the test solution was controlled by the phosphate-citrate buffer.

The solution was kept in contact with the cornea for four minutes. At the conclusion of this time, the tube was removed, and the surface of the eye was thoroughly irrigated with a 1 per cent solution of sodium chloride and the cornea examined for possible damage by means of the fluorescein stain. Then 0.15 cc. of aqueous was withdrawn in a microsyringe and analyzed for the test substance.

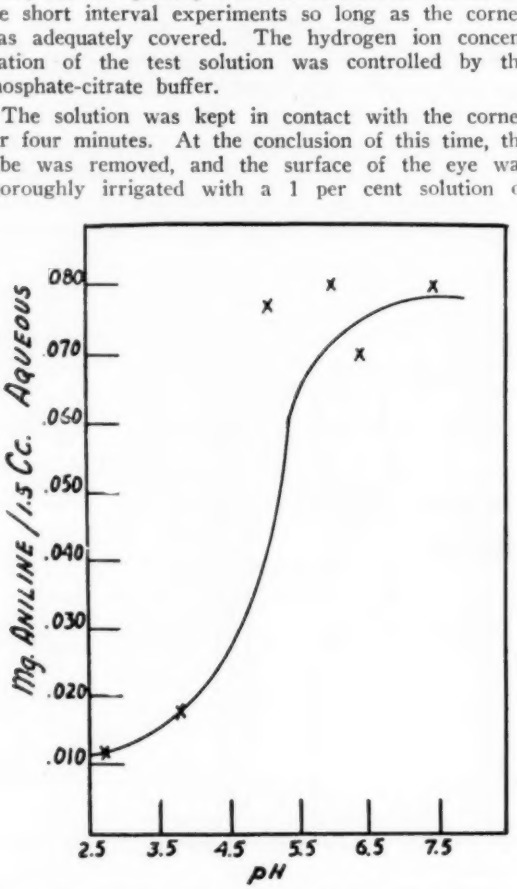

Fig. 4. — Concentration of aniline in the anterior chamber after four minutes when 1 per cent aniline in a 1.5 per cent solution of sodium chloride was placed outside the cornea.

It was first established by means of fluorescein staining that the living rabbit's cornea would tolerate a 2 per cent solution of sodium chloride the p_H of which was controlled within the range of 3 to 12 for contact periods of at least five minutes by buffering with a two-tenths-molar phosphate-citrate solution.

One per cent of aniline in a 1.5 per cent solution of sodium chloride was used as a test solution.

The results are presented graphically in figure 4, each point representing the average of two experiments. It is obvious that the transfer of aniline through the living rabbit's cornea shows the same variation with dissociation as was previously found for the excised cornea.

DISSOCIATION CONSTANTS, SOLUBILITIES AND PERMEABILITIES OF VARIOUS ALKALOIDS

Direct experimental investigation of any large number of alkaloids in a manner similar to that already described for aniline is impracticable in view of the lack of reliable quantitative tests for, and the instability of, most of the alkaloids. Nevertheless, sufficiently accurate tests have been made with atropine, ephedrine and pilocarpine to make it reasonably certain that the results with aniline and salicylic acid are generally applicable provided there are taken into account the dissociation constants and the corresponding changes in solubility in fats and in water. To our knowledge, the dissociation constants of the alkaloids under consideration are only partially available, and data regarding their solubilities in fats (not to be confused with the ordinary organic solvents) are nowhere available. For purposes of reference, therefore, we have undertaken to determine the dissociation constants of some of the alkaloids commonly used and to measure the solubility of each base and of at least one of its salts in water and in tributyrin.

The dissociation constants of the alkaloids were obtained by back titration of the salt with sodium hydroxide. Either the salts were previously purified by repeated recrystallization from cold alcohol until a constant melting point was obtained, or the alkaloid was purified by recrystallization until a constant melting point was obtained and the base was then dissolved in an equinormal solution of an acid and titrated. The p_H at which 50 per cent dissociation occurs was determined by half-neutralization. While this is strictly tenable for the monobasic alkaloids only, it is approximately correct for the polybasic alkaloids (physostigmine and pilocarpine) also; the dissociation constant of the second basic group is negligible for our purposes. The point at which 50 per cent dissociation occurs is familiarly designated by the equation $p_H = 14 - pK_B$ and affords a convenient point of reference for estimation of permeability with variations in the hydrogen ion concentration.

The solubilities of the alkaloids and their salts in water and in tributyrin are given in table 3.

The values for the solubility in water were obtained largely from the Pharmacopeia of the United States [8] and the Merck Index.[9] In the

8. Pharmacopeia of the United States of America, twelfth revision, Easton, Pa., Mack Printing Company, 1942, pp. 604-605.

9. The Merck Index, ed. 5, Rahway, N. J. Merck & Company, Inc., 1940.

case of epinephrine, for which no data were obtainable, the aqueous solubility was determined separately.

The solubilities of the alkaloids in tributyrin were measured as follows:

Sufficient concentrations of the alkaloid were obtained in hot tributyrin so that a precipitation occurred when the solution was cooled to room temperature. Two cubic centimeters of the supernatant tributyrin was then extracted repeatedly with a normal solution of hydrochloric acid until the extractant gave no precipitation with excess ammonium hydroxide. The further procedures were those commonly employed for the purification and determination of alkaloids.[8] The only variation from this procedure occurred in the case of epinephrine, for the identification of which, owing to its low solubility in tributyrin, the more sensitive Viale test was used.

The solubilities of the alkaloid salts in tributyrin were measured similarly except that the aqueous extractant was treated with red mercuric iodide (Valser's reagent) instead of the less sensitive ammonium hydroxide. The extraction was considered complete when the extractant no longer gave a precipitate. Again, the only exception occurred in the case of epinephrine.

The data obtained, presented in table 3, should provide the information necessary to determine what alkaloids approach the optimum conditions for permeability through the cornea.

TABLE 3.—*Solubilities of the Alkaloids in Water and in Tributyrin*

Test Substances	p_H at Which 50% is Dissociated (14 — pK_B)	Solubility, Parts per 100 Cc. of Solvent *	
		Water	Fat (Tributyrin)
Epinephrine		0.01-0.1	0.00003
Epinephrine hydrochloride	8.50	100.0	0.00003
Atropine		0.15	0.28
Atropine sulfate	9.00	250.0	0.007
Cocaine		0.17	9.5
Cocaine hydrochloride	8.62	252.0	0.002
Ephedrine		5.0	33.0
Ephedrine sulfate	9.15	33.0	<0.005
Eucatropine		1.3	0.47
Eucatropine hydrochloride	9.58	>100.0	0.007
Homatropine		1.0-0.1	0.36
Homatropine hydrobromide	9.60	16.6	0.004
Psysostigmine		1.0-0.1	6.0
Physostigmine salicylate	7.7	1.3	0.008
Pilocarpine		100.0-10	Miscible
Pilocarpine nitrate	7.11	25.0	<0.001
Procaine		1.0-0.1	23.0
Procaine hydrochloride	8.90	166.0	<0.005

* The solvent was kept at room temperature (23 C.).

COMMENT

The foregoing data on aniline, salicylic acid and alkaloids indicate that the organic bases penetrate the cornea while their salts do not. This corroborates the previous observation that the corneal epithelium and endothelium are barriers to substances not soluble in fats. There are, however, other considerations which vitiate the immediate application of these results to the local use of drugs. Especially noteworthy is the instability of the aqueous alkaloid solutions unless acidified. Moreover, the tears, having considerable buffer capacity, will determine the hydrogen ion concentration of the weak solution as soon as it is instilled in the eye, so that the p_H of the original solution is not important. Nothing is gained, therefore, by applying solutions of the base, rather than of the salts, to the eye, and much may be lost by decomposition of the drug.

From the practical consideration of permeability through the cornea, some weak electrolytes used in therapy may be considered more suitable than others; it may be possible to synthesize drugs having the optimal prerequisites. The most important considerations for permeability are the dissociation constant and its bearing on fat solubility. The dissociation constant of the "ideal" alkaloid would be sufficiently low so that the alkaloid would be present in the completely undissociated state at physiologic hydrogen ion concentrations. Thus, one would expect pilocarpine and physostigmine to be absorbed through the cornea at p_H 7 more effectively than are atropine, homatropine and ephedrine. A notable exception is epinephrine, which, even in the undissociated state, is practically insoluble in fats.[10] Similarly, the dissociation constant of the "ideal" weak acid would be sufficiently low so that it, also, would be present in the undissociated state at physiologic hydrogen ion concentrations. Obviously, salicylic acid, which was the weak acid most studied, is far from fulfilling this prerequisite.

To the extent that the drug is not present on the cornea in the undissociated state it will, of course, not be efficiently absorbed in the eye, and in passing through the nasolacrimal and the gastrointestinal tract it may be absorbed in sufficient quantity to produce undesirable systemic reactions, such as are common with atropine drops. These factors, which are concerned in the choice of drugs that will penetrate the cornea, do

10. An experiment was undertaken to compare the permeability of epinephrine base and that of a salt of the drug through the excised cornea, but the results were not included in the tables of the text, as they were not quantitative. Little base could be dissolved in the tube fluid, and the Viale test made on the flask fluid after twenty hours merely indicated the absence or the presence of epinephrine in small amounts. Qualitatively, it was apparent that an extremely small amount of epinephrine, even in the form of the base, penetrated through the cornea as long as the epithelium was present.

not appear to have been previously considered in ophthalmic therapeutics.

SUMMARY

1. Permeability through the excised cornea of various weak organic electrolytes (aniline, salicylic acid, atropine, pilocarpine and ephedrine) is a function of the degree of dissociation of the electrolyte. The free base penetrates the epithelium-stroma combination, while the salt penetrates the stroma only. Similar results were obtained with a conjunctiva-sclera combination. This effect of dissociation on permeability is attributed to the difference in solubility in fats and is held to support the previous thesis that substances penetrate the epithelium only so far as they are soluble in fat.

2. Permeability of aniline through the intact cornea in vivo is, similarly, a function of dissociation.

3. A knowledge of the dissociation constant and solubility properties of an alkaloid enables one to predetermine its permeability through the cornea.

Dr. Margaret Holt assisted in measuring the physicochemical constants of the alkaloids and in some of the experiments on permeability.

243 Charles Street.

CARBAMINOYLCHOLINE CHLORIDE IN THE TREATMENT OF GLAUCOMA

DANIEL KRAVITZ, M.D.
BROOKLYN

Until the causes are found, glaucoma, acute and chronic, will be a never ending source of worry to the ophthalmologist, as well as to the patient. The results, even with the best of therapy, all too often are disastrous. Ophthalmologists are therefore on a continuous lookout for new therapeutic methods, both medical and surgical.

In the last few years the greatest advance in the medical treatment of glaucoma has been the synthesis of a large group of cholinergic drugs: mechylol, neostigmine, furfuryltrimethylammonium iodide and, the latest, carbaminoylcholine chloride.

Carbaminoylcholine chloride is a synthetic choline derivative which acts principally by inducing parasympathetic stimulation. Its chemical structure is similar to acetylcholine; and, according to O'Brien and Swan,[1] its action is more prolonged because its hydrolysis is slow and it is therefore more stable in the tissues. Used experimentally on isolated sphincter of the iris, it is one of the most powerful of miotics.

Velhagen [2] found that carbaminoylcholine chloride contracted the sphincter of the pupil in high dilutions, that it reduced intraocular tension and blood pressure and that these effects were antagonized by atropine. According to him,[3] a 0.75 per cent solution of carbaminoylcholine chloride produces greater miosis than a 2 per cent solution of pilocarpine but slightly less miosis than a 0.25 per cent solution of physostigmine. However, he found that a 0.75 per cent solution of carbaminoylcholine chloride had less effect on accommodation than a 2 per cent solution of pilocarpine.

Carbaminoylcholine chloride is also a powerful dilator of the peripheral vascular system. Swan and Hart [4] observed an elevation of temperature in the anterior segment of the eye, indicating an increased blood supply to the part. They found this effect to be greater with this substance than with any of the other cholinergic drugs. Theoretically this action should contraindicate its use in treatment of acute and subacute glaucoma, but clinical experience has not entirely borne out this conclusion.

De Sanctis [5] reported on the effects of carbaminoylcholine chloride on different types of glaucoma. He obtained good results only in cases of chronic glaucoma. The drug had no effect in cases of acute glaucoma even if used in 1.5 per cent solution, but he obtained favorable results in the same cases with neostigmine and mechylol. The reason for the failure may have been faulty application of the drug.

Recently Swan and White [6] have shown that the absorption of carbaminoylcholine chloride through the cornea is inconstant and undependable. If, however, the drug is prescribed in a wetting agent, such as zephiran, its absorptive quality is greatly increased. If, in addition, the eye is massaged through the lids for a few minutes after instillation of the drop, the absorption is further increased.

When used as drops carbaminoylcholine chloride has little effect on the system. However, parenteral administration of too large doses has recently caused a number of deaths. In large doses it causes flushing of the face; vascular dilatation; decrease in blood pressure; increase in pulse rate, basal metabolic rate and respiratory volume; sweating; salivation, and increased peristalsis.

At present, carbaminoylcholine chloride has found its greatest use in treatment of chronic glaucoma, especially in cases in which the dis-

1. O'Brien, C. S., and Swan, K. C.: Doryl in the Treatment of Glaucoma Simplex, Tr. Am. Ophth. Soc. **39**:175-193, 1941.

2. Velhagen, K.: Die Grundlagen der okularen Pharmakologie und Toxikologie des Carbaminoylcholins (Lentin, Doryl), Arch. f. Augenh. **107**:319, 1933.

3. Velhagen, K.: Die praktische Verwendbarkeit des Doryls (Carbaminoylcholin) in der Glaukombehandlung, Klin. Monatsbl. f. Augenh. **92**:472 (April) 1934.

4. Swan, K. C., and Hart, W. M.: Comparative Study of Effects of Mecholyl, Doryl, Eserine, Pilocarpine, Atropine and Epinephrine on Blood-Aqueous Barrier, Am. J. Ophth. **23**:1311 (Dec.) 1940.

5. de Sanctis, G. E.: L'azione del doryl sull'occhio in condizioni normali e in casi di glaucoma, Ann. di ottal. e clin. ocul. **65**:25 (Jan.) 1937.

6. Swan, K. C., and White, N. G.: Corneal Permeability: Factors Affecting the Penetration of Drugs into the Cornea, Am. J. Ophth. **25**:1043 (Sept.) 1943.

ease does not respond to pilocarpine or to physostigmine. It is also valuable as an agent to induce rest when the condition has ceased to respond satisfactorily to these drugs. After a few months' treatment with carbaminoylcholine chloride the eye usually reacts well again to the weaker miotics. The drug has also been used to good effect in aborting an attack of acute glaucoma.[7] It may also be used when other miotics have produced sensitivity of the conjunctiva or dermatitis of the skin of the lids.

The dose varies with each case and must be decided individually. As a rule, a 0.75 per cent solution has slightly more effect than a 2 per cent solution of pilocarpine nitrate and about the same effect as a 0.25 per cent solution of physostigmine salicylate. At first it should be given as often as the other drugs were to be prescribed, and then the frequency of instillation should be reduced. Usually it will be found that the drug can be instilled less often than, and with the same effects as, pilocarpine or physostigmine. This is because it is so slowly hydrolyzed in the tissues and therefore acts for a longer time. Swan[8] showed that when it is prescribed in petrolatum its effects can be still further prolonged, and so it may be instilled less often, with the same results. With carbaminoylcholine chloride, the patient usually complains of greater blurring of vision, and for a longer period than with the other miotics. In some cases this troublesome effect disappeared spontaneously after prolonged use.

REPORT OF CASES

CASE 1.—D. S., a man aged 23, came to the office on Feb. 15, 1942, because of sudden loss of vision in the right eye two weeks before. He had had poor vision since birth. About six or seven years before he consulted me, a cataract had suddenly developed in the left eye. An operation was performed, but vision never returned. Two weeks prior to his consulting me there was sudden loss of sight in the right eye, in which until that time vision had been sufficient to enable him to work. He was now practically blind.

With the right eye large objects were seen as shadows. There was complete aniridia. The lens was swollen and diffusely milky. The eye was buphthalmic, although tension was 20 mm. (Schiøtz). Vision in the left eye was limited to uncertain light perception. There was complete aniridia. A staphyloma involved the ciliary body above. The fundus was not visible. Tension was 3 plus.

The patient was admitted to the Brooklyn Eye and Ear Hospital on March 11 for linear extraction of the lens of the right eye. The postoperative course was uneventful, and he was discharged from the hospital on March 21. On March 29 vision was 20/200 with a correction of + 8.00 D. sph. ⊃ + 3.00 D. cyl., axis 150. On April 2 the patient came to the office stating that he had severe pain in the right eye all night. He said that the same thing had happened to the left eye after operation. Tension was 4 plus, and vision was reduced to perception of shadows. A mixture of 1 per cent physostigmine salicylate and 2 per cent pilocarpine nitrate was prescribed for instillation, but tension could be reduced only to 2 plus. Neostigmine bromide had no better effect. On April 7 the pain had become more severe, and tension was further increased. Carbaminoylcholine chloride, 0.25 per cent, was prescribed, to be instilled every four hours, and the next day tension was reduced to 20 mm. The patient has since been using this substance in the morning and at night only, and the condition has been kept under control. The patient has been able to work at his usual trade.

CASE 2.—H. S., a woman aged 55, came to the outpatient department of the Brooklyn Eye and Ear Hospital, in the service of Dr. Walter V. Moore, on Feb. 25, 1941, because of gradual loss of vision in the right eye.

Examination showed a mature cataract in the right eye, with reduction of vision to shadows. Posterior cortical changes were present in the lens of the left eye. Vision was 20/40 with correction. A complete medical examination revealed nothing pathologic, and no foci of infection were encountered. As vision in the left eye deteriorated rapidly, she was admitted to the hospital for extraction of the right lens.

A combined intracapsular extraction was performed on July 3, 1941. There were no complications at the time of operation, and the postoperative course was uneventful. She was discharged on July 13, with corrected vision of 20/40. On July 26, 1941 tension in the right eye was 50 mm. (Schiøtz), and in spite of the use of physostigmine and pilocarpine, it rose to 65 mm.

On Sept. 7, 1941 cyclodialysis was performed, and the tension dropped to 22 mm. for a few weeks; but on October 11 it was 35 mm. and rose, in spite of the use of miotics, to 65 mm. A second cyclodialysis was therefore performed, on Feb. 2, 1943. The tension dropped to 26 mm. and stayed at that level for several weeks, after which it again rose to 45 mm.

In the early part of March 1943, a prescription for 1 per cent carbaminoylcholine chloride was given the patient, but she continued to use pilocarpine and physostigmine. Finally on Feb. 1, 1944, she decided to have the prescription for carbaminoylcholine chloride filled. The tension promptly dropped to 13 mm., and it has stayed at that level since. At first the drops were instilled every four hours, but at present they are being used three times a day.

CASE 3.—S. G., a man aged 46, came to the office on Oct. 10, 1935, because of difficulty in reading. He had been wearing glasses for over forty years. Vision in the right eye was 20/70 and was improved to 20/20 with correction. He had convergent strabismus in the left eye, a condition which had been present since childhood. Vision in that eye was 20/100 and was improved to 20/70 with correction. Bifocal glasses were prescribed and were checked in November 1939 and December 1940.

He came to the office again on July 13, 1943, because of blurring of the right eye. He stated that for the past several months he had been colliding with people coming from his right. There was no history of seeing halos around lights, but he had occasional episodes of

7. Clarke, S. T.: The Use of Doryl in the Treatment of Glaucoma, Am. J. Ophth. **25**:309 (March) 1942.

8. Swan, K. C.: Carbaminoylcholine Chloride in Petrolatum, Arch. Ophth. **30**:591 (Nov.) 1943.

blurred vision and slight headaches in the right temporal area.

Vision in the right eye was still 20/20 with the glasses previously prescribed. The cornea was moderately steamy, but the pupil was not more dilated than that of the other eye. There were deep cupping of the optic disk and notable contraction of the visual field. Tension was 55 mm. in the right eye and 20 mm. (Schiøtz) in the left eye, with no evidences of glaucoma in the left eye.

A 1 per cent solution of physostigimine salicylate with 2 per cent pilocarpine nitrate was prescribed, and the next day the tension was reduced to 35 mm. Further reduction, however, could not be effected. On July 18 an Elliot trephine operation was done at the Brooklyn Eye and Ear Hospital, and the tension dropped to 18 mm. (Schiøtz). The tension remained at that level until October 10, when it rose to 35 mm. and the field became slightly more contracted. Physostigmine or pilocarpine or the two combined, and later neostigmine, failed to reduce the tension. In fact, it rose three days later to 40 mm., in spite of the presence of a bleb and apparent good drainage.

On December 4 a 0.75 per cent solution of carbaminoylcholine chloride was prescribed, to be instilled every four hours. The tension slowly fell, until by December 16 it was 26 mm. The tension remained at that level until January 21, when it suddenly dropped to 20 mm. It has fluctuated between 25 and 20 mm. since, and the field has enlarged so that it is not more contracted than before the operation.

The patient complained of blurred vision, which lasted almost two hours each time the drops were instilled. Since the early part of March the time of troublesome blurring has been reduced to less than half an hour.

CASE 4.—S. L., a man aged 41, had been under the care of another ophthalmologist for eight years because of chronic glaucoma of both eyes. On June 1, 1943 an Elliot trephine operation was performed on both eyes. The postoperative tension in both eyes remained high, even though the patient had been using a mixture of physostigmine and pilocarpine every three hours since the operation. Because the patient found it too difficult to travel, he came under my care, on Nov. 12, 1943.

Vision was 20/40 in the right eye and 20/30 in the left eye. There was no notable cupping of either disk, and the fields were normal. The tension was 35 mm. (Schiøtz). In order to study the eyes, I asked him not to use the drops for one day. The next day the tension rose to 55 mm. in the right eye and to 45 mm. in the left eye. Administration of the drops was again instituted. The tension fluctuated between 30 and 35 mm., although the instillations were made every three hours.

On November 26, a 0.75 per cent solution of carbaminoylcholine chloride, to be used every three hours, was prescribed. The tension fell rapidly. At present the patient is using an ointment containing 1 per cent carbaminoylcholine chloride at night and 3 drops of the solution in the right eye and 2 drops in the left eye daily. The tension has remained consistently at 25 mm. (Schiøtz). Vision and the visual fields have remained unchanged.

In spite of the frequency of its use, carbaminoylcholine chloride has caused no troublesome blurring. In fact, the patient states that there is a feeling of well-being in the eyes after its use.

CASE 5.—M. T., a man aged 57, came to the office on Dec. 11, 1943, complaining of severe pain in the left eye for about a week. About two years before the patient had an attack of acute glaucoma in that eye, and an iridencleisis was performed by another ophthalmologist. Evidently the tension in that eye had not been reduced by the operation because he had been using a 2 per cent solution of pilocarpine nitrate three times a day. Vision in the left eye had not been good; and about two weeks before his visit to the office the eye became red and painful, and vision was reduced.

Examination of the right eye revealed vision of 20/20 and a tension of 20 mm. (Schiøtz). The left eye was extremely red and the cornea steamy. A knuckle of iris was present under the conjunctiva at 12 o'clock. A hypopyon was present in the lower fourth of the anterior chamber. The fundus reflex was not obtainable, and the eye was soft.

A diagnosis of panophthalmitis was made, and the probability of enucleation was discussed. The patient was admitted to the Brooklyn Eye and Ear Hospital the next day, and large doses of sulfadiazine were prescribed. Several intravenous injections of typhoid-paratyphoid vaccine were also given. On the fourth day a tension of 50 mm. (Schiøtz) developed in the right eye. This was controlled by several instillations of mecholyl chloride and neostigmine bromide. A tension of 20 mm. was subsequently maintained with instillations of a 2 per cent solution of pilocarpine nitrate every four hours. The patient was discharged from the hospital on December 19. The left eye was white, and the hypopyon had entirely disappeared. A large exudate could be seen in the vitreous.

Several days later the patient went to Dr. Mark J. Schoenberg for consultation. While he was at the physician's office, an acute attack of glaucoma developed in the right eye. A bead of ointment containing 1 per cent carbaminoylcholine chloride in anhydrons white petrolatum was placed in the eye, with rapid subsidence of the attack. When the patient was seen the next day at the office, tension in the right eye was 18 mm., although the eye had received no other medication since instillation of the carbaminoylcholine chloride ointment. In this case the drug aborted an attack of acute glaucoma more rapidly, and for a longer period, than any other medicament. A normal tension has since been maintained with instillations of a 2 per cent solution of pilocarpine nitrate every four hours.

The left eye is entirely white; the tension is normal; vision is 20/50—, and there is a fine membrane in the pupillary area. The result is unusually gratifying in a case of late infection after iridencleisis and compares well with other good results in cases of infection following operation.[9]

An unexplained action of carbaminoylcholine chloride has been its relief of pain without reduction of tension in some cases.

CASE 6.—A. S., a woman aged 65, came to the office on March 24, 1944, with a history of sudden onset of pain and loss of vision in the right eye and vomiting. She went to an ophthalmologist, who gave her drops; but the pain was not relieved, and the next day he advised immediate operation.

9. Kravitz, D., and Duest, L. J.: Postoperative Endogenous Infections of the Eye with Recovery, Am. J. Ophth. **27**:167 (Feb.) 1944; correction, ibid. **27**:303 (March) 1944.

Examination revealed that the right eye was red. The cornea was steamy and the pupil only moderately dilated. The fundus was not visualized. The tension was 95 mm. (Schiøtz). The left eye had vision of 20/30 and a tension of 20 mm. Operation was advised, and until the patient made up her mind, an ointment containing 1 per cent carbaminoylcholine chloride, to be instilled into the eye at night before retiring, was prescribed. In addition, she was to use a mixture of pilocarpine and physostigmine, given by the other ophthalmologist, every four hours.

The next day the patient was entirely relieved of pain, though the tension and appearance of the eye were unchanged. She has remained free of pain and now maintains that because there is no pain operation is unnecessary, and she cannot be persuaded to enter the hospital.

CASE 7 (reported by permission of Dr. D. A. Ajello).—M. A., a man aged 67, was first seen on Nov. 4, 1942, with a history of having been treated for glaucoma in both eyes for over three years. He came because of severe pain over the right temporal area and much more severe pain over the left eye.

Examination showed that the patient was completely blind in both eyes. The right eye had a tension of 4 plus. The left eye presented panophthalmitis, with imminent rupture of the cornea. The left eye was removed the next day, and use of miotics in the right eye was continued. The patient continued to complain of severe pain. A few days later there developed a rash on both lids and conjunctival edema. The condition persisted, whether pilocarpine or physostigmine was used. On consultation with me, carbaminoylcholine chloride was prescribed.

The patient was given a 0.75 per cent solution of the drug, to be used three times daily. Within two days the tension was lowered to 2 plus, but he complained of severe pain over the eye for about an hour after each instillation. He was advised to use the drops on arising and just before retiring. Since then he has been entirely free of pain and headaches and of symptoms after instillation of the drops, although the tension remains at 2 plus.

CASE 8.—R. B., a woman aged 59, came to the office on Aug. 15, 1938. She had had an acute attack of glaucoma in the left eye the evening before. Her son, who is a physician, recognized the symptoms and immediately and repeatedly instilled a 0.5 per cent solution of physostigmine salicylate, so that when I saw her, the tension was 16 mm. in that eye and 20 mm. in the right eye (Schiøtz). The pupil was moderately and irregularly dilated, and the eye was somewhat tender to touch but was of normal appearance. The visual fields were normal. Vision was 20/30 in the right eye and 20/25 in the left eye with correction.

The patient was seen at regular intervals. The pressure in the left eye fluctuated between 35 and 22 mm. (Schiøtz), but the fields and vision remained good. However, the disk began to appear cupped as time went on.

On Feb. 1, 1940, an Elliot trephine operation was performed on the left eye at the Beth Moses Hospital, after which the pressure dropped to 20 mm. The pressure in the eye has remained at that level, and the fields and visual acuity have not changed.

On Sept. 14, 1939 the tension in the right eye rose to 30 mm. (Schiøtz). This was easily controlled with a 2 per cent solution of pilocarpine nitrate, instilled four times a day. Inasmuch as vision remained good and the fields were unchanged, conservative treatment was followed.

During January 1941 the right disk began to appear cupped, and operation was advised. This the patient refused because her son had just joined the armed forces, and so she was kept under close observation. The tension in that eye fluctuated between 30 and 22 mm.; but vision remained unchanged, and the fields were only slightly constricted.

On Sept. 2, 1943 a severe attack of acute glaucoma developed. The eye was stony hard and could not be reduced by miotics of any kind. The next day a basal iridectomy was done at the Brooklyn Eye and Ear Hospital, with a good immediate result.

On October 11 the lens began to swell and the tension to rise. These symptoms became rapidly worse, so that an extracapsular extraction was necessary. This was done at the Brooklyn Eye and Ear Hospital on Nov. 12, 1943. Remnants of capsule remained in the anterior chamber and could not be removed. Healing was uneventful. The tension remained normal until Jan. 31, 1944, on which day she complained of a pain in the eye and a feeling as if there were a lump on the eye. The tension was 60 mm. (Schiøtz).

A 1 per cent solution of carbaminoylcholine chloride, to be used every four hours, was prescribed. The next day the sensation of a lump and the pain had entirely subsided, but the tension was unaffected. Since then the tension has varied from 40 to 70 mm., but at no time has the patient had any discomfort in that eye.

CONCLUSION

Carbaminoylcholine chloride is not a panacea for all the ills of glaucoma. The cases here presented are fairly representative of almost all the forms of glaucoma that may be encountered. The drug has been effective in relief of all types. In some cases, however, it has not produced good results. In a case of glaucoma following an intracapsular extraction, in the service of Dr. Walter V. Moore, the intraocular tension rose during treatment with carbaminoylcholine chloride. However, no other medication had been effective, and subsequently a cyclodialysis was performed.

Carbaminoylcholine chloride is a valuable addition to the armamentarium for the treatment of glaucoma, and it may give brilliant results when other drugs have failed. Because of the troublesome and prolonged blurring, and sometimes pain, following its use, pilocarpine, physostigmine, mecholyl and neostigmine should first be tried.

861 Park Place.

LIPOCHONDRODYSTROPHY

(DYSOSTOSIS MULTIPLEX; HURLER'S DISEASE); PATHOLOGIC CHANGES IN THE CORNEA IN THREE CASES

LIEUTENANT MICHAEL J. HOGAN (MC), U.S.N.R.,
AND FREDERICK C. CORDES, M.D.
SAN FRANCISCO

Lipochondrodystrophy is a rare disease of congenital origin and uncertain cause. It is characterized by chondrodystrophic changes in the skeleton and deposition of a lipid-like substance in many of the body tissues, including the cornea.

The first signs of the disease usually appear toward the end of the first year of life, when dorsolumbar kyphosis and enlargement of the head make their appearance. As the condition progresses numerous developmental failures appear. The child learns to walk, talk and feed itself at a later age than normal. By the age of 4 years normal growth has usually ceased, and the complete picture of the disease has become apparent. The head is enlarged; the face shows wide-set, protuberant eyes and a saddle nose and there is thickening of the lips and tongue. The neck is very short and the chest poorly developed. There are a protuberant abdomen, with an umbilical hernia, and enlargement of the liver and spleen. The joints of the hands, wrists, elbows and hips present deformities and limitation of motion. The hands are broad and thick. These bodily changes give the child a gargoyle-like appearance.

Roentgenographic studies show characteristic changes. The skull is usually enlarged and scaphocephalic. In a large number of cases the sella turcica is greatly elongated, due to maldevelopment of the sphenoid bone. Irregularities, fragmentation and enlargement of the ends of the shafts of the long bones are almost always noted. There is dorsolumbar kyphosis, with narrowing and flattening of the vertebral bodies in this portion of the spine. A distinctive clouding or haziness of the corneas occurs in over 75 per cent of cases. When it is present, it is considered diagnostic of the disease. In most cases this cloudiness appears before the age of 3 years. Instances have been reported in which it was present at birth. On inspection with focal illumination the corneas have a ground glass appearance and are diffusely hazy. There is no tendency for the eye to be inflamed or for the cornea to become vascularized. With the slit lamp the haze is resolved into uniformly distributed tiny, gray or yellow-gray dots, which at first occupy the middle and deeper layers of the cornea. Later they are distributed throughout the stroma. These dots do not appear to be crystalline and are only slightly refractile. After a certain stage of opacification is reached, the cornea remains unaltered. Vision is reduced correspondingly as the opacification proceeds. Hyaline or calcareous degeneration of this material in the cornea has not been reported. The intraocular tension is usually normal. Studies of the blood fats usually reveal no abnormality.

PATHOLOGIC CHANGES

There are three published reports in the literature of pathologic studies of the eyes in cases of lipochondrodystrophy.

The first report was made by Kressler and Aegerter,[1] in 1938. In their case all the signs of lipochondrodystrophy were presented. Clouding of the corneas was first noted by the parents when the child was 4½ months of age. The authors first examined the patient at the age of 6½ years, at which time the corneas were opaque. The child died of heart disease at the age of 7½ years. At autopsy all the organs except the kidneys showed extensive fatty infiltration. Many of the ganglion cells of the cerebral cortex, the basal ganglions and the brain stem were balloon shaped, with puffing of the axons and dendrites. The cytoplasm had a netlike structure, in which there were fine, dark blue granules which did not take stains for fat. The glia cells of the cortex contained lipid, as did those in the white substance. Many attempts were made to stain the material which produced vacuoles in the cells of all the other tissues. The results, however, were not conclusive.

Histologic examination of the eyes showed that the laminas of the cornea proper were widely separated and that there was no cellular infiltration. The authors were uncertain as to whether this separation was an artefact secondary to fixation or the result of edema or infiltration. All the other ocular structures appeared normal. The report did not state whether any attempt was made to stain the corneal tissues for fat.

From the Division of Ophthalmology, University of California Medical School.

This study was made possible by a fund from the Mrs. E. S. Heller Donations.

1. Kressler, R. J., and Aegerter, E.: Hurler's Syndrome (Gargoylism), J. Pediat. **12**:579, 1938.

The second report was made by Berliner,[2] in 1939. His patient died at the age of 5 years, after repair of an umbilical hernia. A photograph of the patient demonstrates all the typical features of lipochondrodystrophy. Examination showed extensive opacification of all the corneal layers, without vascularization. Vision was approximately 10/200 in each eye. The intraocular tension measured 14 mm. of mercury (Schiøtz) in each eye, and the corneas appeared larger than normal. Pyroxylin sections of the eye were prepared and stained by various technics. Stains of gelatin mounts of corneal sections for neutral fat gave negative results. The deeper and central areas of the cornea, corresponding to the main opacification seen clinically, gave a paler reaction to all the stains. Bowman's membrane was missing in places and was replaced by cells containing a vacuolated cytoplasm, the cells varying from spindle shape to globular. The corneal nuclei lay in spindle-shaped, vacuolated spaces. In the deeper, central regions of the cornea these vacuolated spaces contained granular material. Berliner expressed the opinion that this material was composed of lipid granules and that the presence of these granules refuted any claim that the spaces were the result of artefacts. The granules were well brought out with Masson's stain and with hematoxylin and eosin and were similar in appearance to those observed in other organs. The rest of the eye showed no abnormality.

The third pathologic report was made by Rochat,[3] in 1942. In his case, which had been reported previously (1940) from the clinical standpoint by Waardenburg,[4] pronounced diffuse clouding of the corneas, together with all the other changes charactertistic of lipochondrodystrophy, was present. Waardenburg removed one eye at autopsy and sent it to Rochat for pathologic examination. The eye was fixed in a dilute solution of formaldehyde. One portion was used for frozen sections, and the other was embedded in paraffin. The only changes encountered in the eye were those in the cornea. The corneal epithelium and stroma and Descemet's membrane were normal. In Bowman's membrane, however, numerous defects were scattered across the whole cornea. In these defects were large cells containing abundant protoplasm and well stained nuclei. The protoplasm contained numerous glistening granules. At times these granules were confluent, producing the appearance of snowflakes. The granules were soluble in ether and alcohol but were not doubly refractile in polarized light. The usual reactions for fat with osmic acid and sudan III were negative. At times two corneal lamellas were separated, and the resulting space was filled with large granular cells of the same type. Rochat stated that these cells resembled the so-called foam cells which are present with cholesterol in atrophic or old hemorrhage-filled eyeballs. He concluded these cells were not to be considered the primary factor in the production of the defect in Bowman's membrane but were the reaction of the body to a deposit of lipid substances. He did note, however, scattered swollen corneal corpuscles containing granules but could not be certain whether or not these changes were of postmortem origin. None of the other glassy membranes of the eye showed changes similar to those seen in and near Bowman's membrane.

2. Berliner, M. L.: Lipin Keratitis of Hurler's Syndrome (Gargoylism or Dysostosis Multiplex): Clinical and Pathologic Report, Arch. Ophth. **22**:97 (July) 1939.

3. Rochat, G. F.: The Corneal Changes in Dysostosis Multiplex, Ophthalmologica **103**:253, 1942.

4. Waardenburg, P. J.: Hurler's Dysostosis Multiplex, with Special Reference to the Ocular Symptoms, Ophthalmologica **99**:307, 1940.

REPORT OF CASES

The following study was made of the eyes of 3 patients who died with lipochondrodystrophy. The cases of 2 of these patients were included in a previous clinical report on this disease.[5] Dr. Theodore Holstein of Boise, Idaho, furnished the specimen, together with the clinical history in the third case and gave us permission to report the case.

Fig. 1.—Patients in cases 1 and 2, showing typical changes of lipochondrodystrophy.

CLINICAL DATA

CASE 1.—J. P. P., a boy, born July 8, 1935, was first seen at the University of California Hospital on Oct. 3, 1940 on admission to the clinic for study and observation.

History.—He was a normal full term child at birth. There was no consanguinity in the family of either parent. The mother noted the appearance of lumbar kyphosis when the child was 5 months of age. The typical facies commenced to develop at the age of 1½ years, and by the age of 3 years the boy demonstrated most of the features of lipochondrodystrophy, with dwarfing, deformities of the extremities and corneal cloudiness.

5. Cordes, F. C., and Hogan, M. J.: Dysostosis Multiplex (Hurler's Disease: Lipochondrodysplasia; Gargoylism), Arch. Ophth. **27**:637 (April) 1942.

Examination.—The appearance of the child was typical of lipochondrodystrophy. The head was large, and the face showed wide-set, protuberant eyes. There was a saddle nose, and the lips and tongue were thickened. He was almost deaf. There were protuberance of the abdomen, umbilical hernia and enlargement of the liver and spleen.

Ocular Examination.—There was esotropia of the left eye of 10 degrees. Visual acuity could not be determined. Each cornea measured 13 mm. in diameter. A uniform haze was seen in each cornea, without any sign of ocular inflammation or tendency to corneal vascularization. Examination with the slit lamp showed a uniform distribution of gray punctate spots throughout the corneal stroma. The intraocular tension could not be obtained with the tonometer but seemed normal on palpation.

Course.—The patient was observed in the clinic for some time and was then committed to the Sonoma State Home. He died there Feb. 1, 1942, at the age of 6½ years.

Autopsy showed pulmonary tuberculosis as the primary cause of death. The pathologist excised both corneas, placed them in a 10 per cent concentration of solution of formaldehyde U. S. P. and forwarded them to the department of ocular pathology of the University of California Hospital.

CASE 2.—D. P., a boy, born Feb. 13, 1937, a brother of the patient in case 1, was also first seen at the University of California Hospital on Oct. 3, 1940 on admission to the clinic for study and observation.

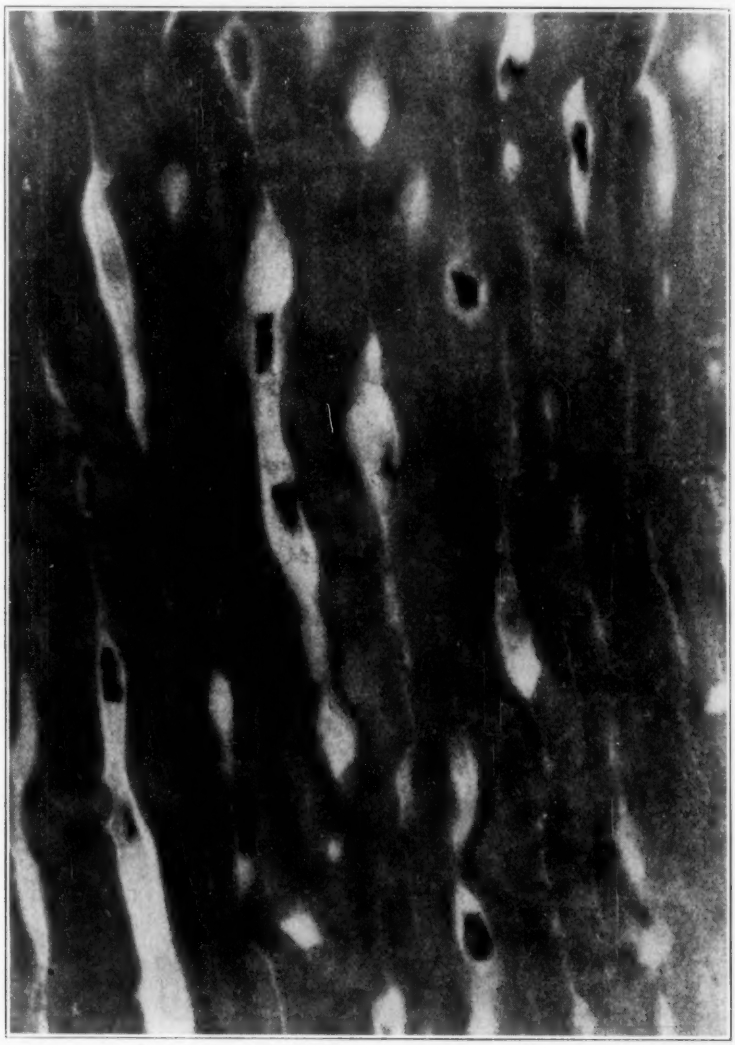

Fig. 2 (case 1).—Frozen section, showing swollen, granular corneal corpuscles. High power lens; hematoxylin and eosin stain.

History.—The patient was a dissimilar twin, whose sister developed normally. The first signs of the disease appeared at the age of 5 months, when lumbar kyphosis was noted. At 1 year of age the head was enlarged, and the hands were broad and thick, with flexed, stiffened fingers. The general similarity to his older brother was notable at this time. He presented the complete syndrome of lipochondrodystrophy at the age of 3 years, and his development was much retarded. He could not talk at that time.

Examination.—All the classic features of lipochondrodystrophy were present. The head was large, with prominent frontal bosses. The eyes were wide set and protuberant, and there was a saddle nose. The abdomen was protuberant and showed a large umbilical hernia. Palpation revealed an enlarged liver and spleen. There was pronounced dorsolumbar kyphosis.

Ocular Examination.—There was mild exophthalmos. Visual acuity did not seem to be impaired, and palpation showed normal intraocular tension. The cornea of each eye measured 13.5 mm. in diameter. Examination of the corneas with oblique illumination showed them to be fairly opaque, like ground glass. Examination with the slit lamp revealed the typical grayish punctate dots scattered throughout the stroma of the cornea, but more conspicuous in the deeper layers. Roentgenographic examination showed most of the typical features of lipochondrodystrophy.

Course.—The patient was observed, likewise, in the clinic for a period and was subsequently committed to the Sonoma State Home. He died of an infection of the respiratory tract about two months after his older brother, at the age of 5 years. The corneas were removed at autopsy, fixed in a 10 per cent concentration of solution of formaldehyde U. S. P. and forwarded to the department of ocular pathology.

CASE 3.—R. S., a boy aged 5 years, an only child, was first brought to Dr. Theodore Holstein, of Boise, Idaho, in the early part of 1942 because the parents thought the child was blind. The peculiar features of lipochondrodystrophy appeared during the first year of life, when the corneas gradually became cloudy. By the age of 2½ years the child had a large head, and the eyes were wide set and protuberant. The lips were thick, and he was a mouth breather, as a result of the saddle nose. The abdomen was considerably enlarged. He died April 11, 1942, at the age of 5 years, of hydrocephalus. The right eye was removed at autopsy, placed in a 10 per cent concentration of solution of formaldehyde U. S. P. and sent to the department of ocular pathology.

Fig. 3 (case 1).—Paraffin section, showing thinning of Bowman's membrane and cellular infiltration. Low power lens.

PATHOLOGIC STUDY

Technic.—The specimens in cases 1 and 2 were sent to us from the Sonoma State Home. There was delay in fixation of the tissues, which accounted for the postmortem changes seen in the slides. The corneas in cases 1 and 2 were fixed for forty-eight hours in 10 per cent concentration of solution of formaldehyde U. S. P., after which they were divided in three portions with sharp scissors. One portion was used for frozen sections; one was embedded in paraffin, and the third portion was used for paraffin sections, and the remainder of the eye was embedded in pyroxylin and cut in the usual manner. The stains used on this eye were the same as those employed in cases 1 and 2.

Chemical analyses for fats and fatlike substances were not made because the tissue had been fixed in a solution of formaldehyde and was therefore not considered suitable.

Observations.—Cases 1 and 2: The changes in the corneas in these cases were similar; so they will be

Fig. 4 (case 1).—Complete replacement of Bowman's membrane by the large cells. High power lens.

was embedded in pyroxylin. The portion which was used for frozen sections was cut in the usual manner, and the sections were stained in a variety of ways for neutral fats and lipids, as well as by the usual hematoxylin and eosin method. Routine preparations with hematoxylin and eosin and with the Masson stain were made of the sections embedded in paraffin and pyroxylin.

The eyeball in case 3 was already well fixed in solution of formaldehyde U. S. P. on arrival. Large calottes were cut from the superior and inferior portions. The cornea attached to the calottes was excised, and a portion was used for frozen sections. Another

described together. Postmortem changes were evident throughout the cornea, but not to a notable degree. The epithelium was missing in some areas and partially desquamated in others, but that which remained was normal. The endothelial cells were also missing in some areas, but when present they seemed normal.

The principal changes encountered in the corneas were in the region of Bowman's membrane and in the corneal corpuscles. Most striking were the changes near and in Bowman's membrane. A great number of large polygonal or rounded cells were dispersed beneath this membrane across the whole cornea. In some areas,

where the infiltration of cells was pronounced, Bowman's membrane had become considerably thinned. There were numerous breaks in the membrane, and these dehiscences were filled with cells. The cells had an abundant, granular cytoplasm, and the nuclei were often eccentric. The granules in the cytoplasm were fine and stained darkly with hematoxylin. In frozen sections the granules were abundant throughout the cytoplasm, but in paraffin and pyroxylin sections they were almost entirely absent. The cytoplasm appeared vacuolated or honeycombed in the latter preparations, the picture being similar to that observed after phagocytic cells lose their fat on being treated with solvents. Frozen sections prepared with sudan IV and other stains for lipids showed that these granules did not accept fat stains.

Of next greatest interest were the changes in the corneal corpuscles. The corpuscles and their processes were considerably swollen. The cytoplasm of the cells and processes contained a large amount of fine granular material, similar to that seen in the cells near Bowman's membrane. This material, too, was partially removed from the cell when the tissues were treated by the usual technics for embedding in paraffin and pyroxylin, and it remained in the frozen sections. Stains for fat gave negative results in the corpuscles.

One might consider that part of these changes in the corpuscles were due to postmortem degeneration, but we have not observed such conspicuous alterations in other eyes which were fixed late.

CASE 3.—Gross examination of the eye showed that it was of normal shape. The cornea was diffusely cloudy and measured 12 mm. in diameter. The globe measured 24 mm. in length, 25 mm. in the horizontal diameter and 25 mm. in the vertical diameter. Calottes were cut from the superior and inferior portions. The intraocular contents appeared normal.

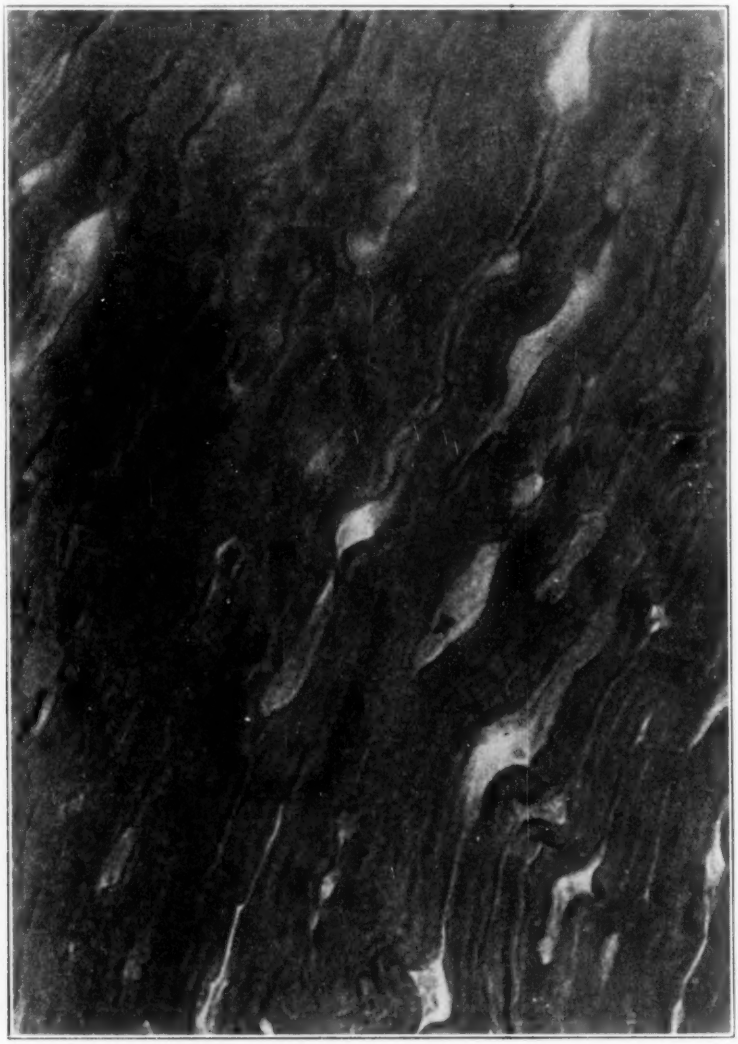

Fig. 5 (case 2).—Swollen corneal corpuscles. High power lens.

Microscopic examination showed the same corneal changes as those encountered in cases 1 and 2, but to a lesser degree. The area beneath Bowman's membrane revealed a considerable number of large phagocytic cells. Bowman's membrane itself was less affected; but a number of complete breaks in its structure were encountered, and these dehiscences were filled with phagocytes. The phagocytes all had an abundant cytoplasm, which in frozen sections appeared filled with fine

granules. These granules were almost completely dissolved out in the paraffin and pyroxylin sections. The granules failed to take any of the stains for fat. The corneal corpuscles were also affected, showing numerous granules in their cytoplasm, but the process seemed less diffuse than that in cases 1 and 2.

There were numerous phagocytes of considerable size in the lamellas near the periphery of Descemet's membrane. The phagocytes could also be seen in the anterior trabecular meshwork. The material in the cytoplasm of these cells reacted similarly to that in the cytoplasm of the corneal phagocytes and corpuscles. Numerous phagocytes were also noted in the stroma and on the anterior surface of the iris.

All the remaining ocular structures were normal except for the retinal and the optic nerve, which were atrophic. This change was considered secondary to the hydrocephalus.

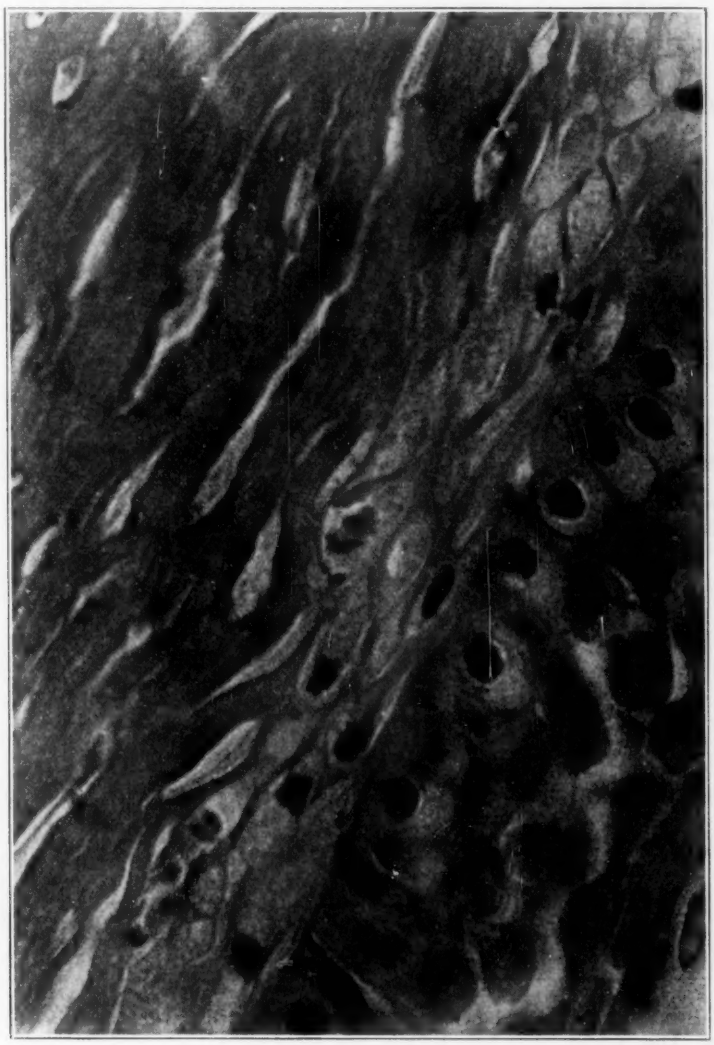

Fig. 6 (case 2).—Pyroxylin section, showing swollen corneal corpuscles and complete replacement of Bowman's membrane by histiocytes at this point. High power lens; hematoxylin and eosin stain.

COMMENT

From a histologic point of view, the corneal changes encountered in the region of Bowman's membrane confirm the observations of Berliner and Rochat. In each case the infiltration of large phagocytic cells was noted beneath the membrane, and it was also seen that these cells contained an abundant cytoplasm which was filled with a fine granular material. Our observations confirm those of Rochat in that this granular material was dissolved out of the cytoplasm when the tissues were treated with fat solvents. In none of the reports is there evidence that the material in the cells was of a fatty nature: Berliner and Rochat commented that stains for fat gave negative results, and we were unable to stain the material in any of our sections.

Sections of tissues from our 3 cases were sent to other pathologists for comment. Dr. Georgiana Theobald noted the infiltration of phagocytic cells in the region of Bowman's mem-

brane but stated that one should not assume that the material in the cells was of fatty nature. Dr. L. von Sallmann made the following comment:

The sections in these cases show the same vacuolated cells in the superficial layers of the cornea, with partial replacement of Bowman's membrane, as were described by Berliner and Rochat. However, they present much more postmortem change than did Berliner's sections. The granular deposits in the stromal cells of the cornea resembled those described by Berliner. The lipid nature of the granules is, I think, not proved beyond doubt, even though it is assumed.

Dr. Alson Braley stated:

All the slides show considerable postmortem change, and the cells, especially the large phagocytic cells, are difficult to distinguish. According to the description by Berliner, the histologic picture of this disease is fairly typical, and in none of the cases of lipochondrodystrophy so far described have the phagocytes in the cornea given a positive stain for neutral fat. It is possible of course that this material is lipid in nature.

There is considerable evidence that the corneal corpuscles are involved in this disease. Both Berliner and Rochat noted that these corpuscles contained a granular material. Berliner was sure of its presence, but Rochat could not be certain whether or not it was a postmortem change. Our observations seem to indicate that there is actually an infiltration of the corpuscles.

The nature of this material in the cells is undetermined. Six autopsy reports are available for study. In almost all the cases the brain, pituitary, thyroid, testis, liver, spleen, endocardium, adrenal glands, osteoblasts and endosteal cells were reported to be infiltrated with a foreign material. The normal tissue cells seem to imbibe the material in most instances and become greatly swollen, with a granular cytoplasm. In this respect lipochondrodystrophy differs from the other lipodystrophies in that the fatty substances in the latter (Hand-Christian-Schüller, Niemann-Pick and Gaucher disease)

Fig. 7 (case 3).—Pyroxylin section, showing cellular infiltration in the trabecular area near the end of Descemet's membrane. Low power lens; hematoxylin and eosin stain.

are present in the tissues in phagocytic cells. Our observations on the eyes in the present cases indicate that the substance in the tissues of patients with lipochondrodystrophy is present in phagocytes, in addition to the normal tissue cells. Examination of the other organs of the body in cases 1 and 2 confirms most previous pathologic studies. In the absence of chemical studies on the tissues in this disease, it is necessary to assume that the foreign material in the tissues is of fatty nature, even though it does not react to the usual stains for fat.

Correlation of the clinical data and the pathologic changes in the corneas in the present cases leads to the assumption that the numerous corneal opacities seen grossly and with the slit lamp are produced by the infiltration of phagocytic cells into the region of Bowman's membrane and by the swelling of the corneal corpuscles. There is no other cellular or fluid extravasation into the stroma to account for them.

CONCLUSIONS

In the pathologic examination of the eyes in 3 cases of lipochondrodystrophy, the corneal changes were found to be confined to the region of Bowman's membrane and to the corneal corpuscles.

The corneal opacities seen clinically are caused by (*a*) infiltration of numerous large phagocytic cells into the region of Bowman's membrane, causing thinning and ruptures in the membrane, and (*b*) swelling of the corneal corpuscles.

The phagocytic cells near Bowman's membrane and the corneal corpuscles show numerous fine granules in their cytoplasm. These granules are present in frozen sections but are removed by fat solvents, an indication of their possible lipid nature. The granules, however, do not take the usual stains for fat.

384 Post Street.

HEAT AND COLD IN THERAPY OF THE EYES

F. H. RODIN, M.D.
SAN FRANCISCO

Heat and cold have been used as therapeutic agents from time immemorial. Although they are universally employed in the treatment of various conditions of the eye, the difficulties and hazards of adapting them to oculotherapy have kept them from earning the popularity they deserve. Essential requirements are that the desired agent be readily obtainable, easily prepared and applicable with minimum discomfort and maximum benefit. To date no satisfactory simple method has been reported in the literature. The purpose of this paper is to present a procedure that has given gratifying results.

HISTORY

Early in the history of medicine, Hippocrates (460 B. C.) wrote: "Diseases of the eye are cured by drinking wine, or by baths, or by fomentation, or by bleeding, or by purifying medicines." These principles were adhered to by his followers until Celsus (25 A. D.) voiced a problem which even today has not been fully solved.

> Concerning the application of fluid, the question is raised whether cold compresses are more appropriate than warm ones. In cases accompanied by pain, internal suppuration, itching, tears without running sores, warm compresses are more advantageous. In cases where there is only a slight amount of pain or where there is marked redness, cold compresses should be used.

Celsus advocated hourly application of compresses and the use of a small amount of water. At his instigation the sea sponge sometimes replaced the compress.

Treatment by steam or fumes is also of ancient origin. The Greek conception was to expose the open eyes to the vapor of a boiling eagle's liver until perspiration was induced. The Arabs preferred the steam from heads of sheep for the treatment of snow blindness, and fumes from the boiling flesh of wild donkeys was widely prescribed. The antiphlogistic properties of various plants in infusion and of resin from certain fruit trees were extolled in Galen's era (130 A. D.). A few of the more popular remedies of that time were rubbing the eye with substances such as amber, gold, pearls and coral; ingestion of certain foods; baths; bleeding, and cupping. Turpentine and powdered cantharides were used as irritants, and extensive use was made of animal gall. Decoctions of lentils were supposed to act favorably on the lens, and lentil porridge and baked apples were employed as fomentations. Among the more curious remedies may be mentioned saliva, breast milk and powdered grasshoppers, while old beer and wine were utilized as vehicles, as well as butter, lard and honey (sixteenth century).

HEAT

The effect of heat on certain ophthalmopathies, particularly when external, is twofold—analgesic and therapeutic. Heat is a vasodilator, producing increased hyperemia in inflamed tissues, which not only affords comfort to the patient but hastens the process of repair by accelerating metabolism and leukocytosis. It is recommended for mild keratitis, particularly of the phlyctenular type; mild blepharitis; acute conjunctivitis; corneal ulcer, and many intraocular disorders. In the preoperative care of patients with glaucoma it affords singular relief. It also plays an important role in the therapy of acute dacryocystitis and is beneficial in the treatment of acute glaucoma and of iridocyclitis, scleritis, episcleritis and other inflammations. In the case of conditions unidentified with pain, such as turbidity of the vitreous, intraocular hemorrhage and choroidal disease, it promotes recovery.

One of the readiest and most efficient agents is hot water, usually applied in the form of moist compresses. Hydrotherapy has encountered both favor and disfavor among ophthalmologists throughout the centuries, disfavor accruing in large part from the complicated systems in vogue. It was von Gräfe [1] who revived the use of heat in modern times and enthusiastically advocated it as a curative measure. The literature abounds in descriptions of mechanical devices that have been recommended for this purpose, such as Leiter's coils, the Japanese hot box and specially

From the Department of Ophthalmology of Mount Zion Hospital, and the Division of Ophthalmology of Stanford University School of Medicine.

1. von Gräfe, A.: Anwendung lauer und warmer Überschläge bei gewissen Ophthalmien, Arch. f. Ophth. **6**:133-150, 1860.

shaped water bags. Only a few of the less complicated methods will be reviewed here.

Methods of Application.—Conner [2] fully described the use of hot water in the treatment of disturbances of the eyes and deplored the paucity of scientific literature on this form of therapy. He stressed the potency of hot water, unsupported by other measures, in promoting nutrition in tissues involved in a disease process, in removing causal organisms and in encouraging healing. He also went so far as to state that the reaction to heat of any pathologic condition of the eye was one of great improvement. Conner suggested that the patient bend his head over a bowl of hot water and throw the water gently with his hands over the affected eye without touching it. Since this method was rather tiring and the water could not be kept hot enough, he devised a pint-sized rubber bulb containing a thermometer, with an opening at the top to fit the patient's eye. A sustained even temperature was made possible by a stopcock-regulated flow of hot water through a tube attached to the top of the bulb and drainage of the cooled water from the bottom. Although the results were excellent, the apparatus was costly and unsuited to individual requirements; so it never came into general use.

Another ingenious method of using hot water described by Conner was to construct a clay dam on the patient's face while he was supine, so that when hot water was poured into the ocular cavity the eye was completely immersed. Thermometer readings enabled a constant temperature to be maintained, and drainage tubes disposed of the cooled water. The continuous, cautious supervision that this system demands has prevented it from becoming a routine procedure.

The third, and simplest, method recommended by Conner [3] provided direct contact with hot water by the medium of an ordinary water glass. A dam was produced by the rim of a filled glass held against the face and the side of the nose underneath the eye. With the head inclined forward the eye was completely submerged. The desired degree of heat could be maintained by replenishing the water in the glass. A further advantage was that antiseptics could be added if indicated.

Hotz, in discussing Conner's paper, stated that sensation informs the patient at what temperature the water is to be kept. He emphasized the efficacy of heat in reducing venous congestion of the anterior part of the eyeball; he claimed that the type of application was of secondary importance.

Wood [4] recommended the application of hot, moist compresses composed of strips of flannel or several thicknesses of gauze, wrung practically dry in water as hot as the eye could comfortably tolerate and changed the moment they began to cool. An alternative compress was a small towel or washcloth folded about 3 inches (7.5 cm.) wide and 18 inches (45 cm.) long. Holding one end in each hand, the patient dipped the cloth into water as hot as he could stand and applied it to the closed lids and the surrounding area. For best results the compresses were renewed every few minutes during the prescribed period.

Franke [5] offered the following technic of applying heat: Five to ten folds of bandage, or enough white linen or cotton material to cover the eye and vicinity, is soaked in the hot solution; the excess water is expressed gently, and the compress is applied to the closed eye. A compress of this type retains its heat only briefly, and as the aim of thermotherapy is to provide and maintain a fixed, unvarying temperature, additional compresses should be prepared for immediate replacement of the one removed.

The procedures for the use of hot compresses as described in textbooks for nurses are usually elaborate and consume considerable time in preparation and application. This is well illustrated by the method described by Denison and Eklund: [6]

Equipment: The necessary equipment for the application of hot compresses is:

Foment cup
Boric solution 1:50
2 wooden throat sticks
8-12 cotton balls
Boric ointment or vaseline [petrolatum] (to protect the skin)
Foment mat or small enamel tray

Procedure: The boric solution, throat sticks, and cotton balls are placed in the foment cup and boiled for five minutes. The cup of hot solution is then placed on a protecting mat at the patient's table.

If there is any discharge, the nurse should wash off the patient's eye with warm boric solution and then,

2. Conner, L.: Use of Hot Water in Local Treatment of Diseases of the Eye, Am. J. M. Sc. **82**:466-472, 1881.

3. Conner, L.: Hot Water in Management of Eye Diseases: Some Suggestions, Tr. Internat. M. Cong. **3**:673-681, 1887.

4. Wood, C. A.: A System of Ophthalmic Therapeutics, Chicago, Cleveland Press, 1909, pp. 81 and 84.

5. Franke, E.: Ocular Therapeutics: A Manual for the Student and the Practitioner, St. Louis, C. V. Mosby Company, 1925, pp. 98-100.

6. Denison, A.-H., and Eklund, L.: A Textbook of Eye, Ear, Nose and Throat Nursing, ed. 2, New York, The Macmillan Company, 1937, pp. 123 and 124.

with a throat stick, apply a thin film of boric or some form of ointment to the lids and surrounding area to protect the skin.

The nurse should apply the foments on all children and old, feeble individuals. With the latter exceptions, intelligent patients may be taught to do this procedure very satisfactorily.

The patient is instructed to lift one cotton ball from the container with the throat stick and to squeeze out the solution with the blade of the other boiled throat stick. The steaming, moist pledget is held near the eye until it can be tolerated directly on the lid. Each cotton ball is discarded after use. The duration of the treatment is approximately eight minutes for usually after this, the solution is not sufficiently hot to be effective. If prolonged application is required, the solution must be reheated at intervals. For constant hot applications, an electric stove plugged in at the bedside is very convenient.

From the preceding description it is evident that the methods recommended are cumbersome, require special equipment and are not altogether safe.

COLD

Cold, like heat, has a twofold effect—analgesic and therapeutic. Cold is a vasoconstrictor, producing anemia in chemotic and congested tissues, an action which is soothing to the patient and accelerates the process of repair. Cold applications lack the popularity enjoyed by hot ones, probably because less is known of the specific indications for their use and of their therapeutic effects, and because of the distaste frequently displayed toward them by patients. Nevertheless, they hold an important place in oculotherapy and are recommended for the relief of lesions produced by physical or chemical trauma, early conjunctivitis, blennorrhea and acute trachoma and for postoperative care.

Methods of Application.—Wood suggested the application of iced compresses made of seven or eight thicknesses of gauze or of absorbent cotton about 2½ inches (6 cm.) in diameter. The flat, smooth surface of a block of ice was covered with six of these pads. When thoroughly saturated, they were wrung out as needed and applied to the eye. Ice water running down the face is unpleasant and may be avoided by careful removal of all excess water before application of the compress. Frequent changes were advised, as the inflammation rapidly imparts heat to the pad. Replacements were made with as brief an exposure of the affected area as possible. Wood recommended the folded towel compress dipped in a basin of cold or ice water for cold therapy. He advised a shorter period of application and a longer interval between applications and immediate discontinuation or replacement by hot fomentations if the cold compresses caused pain or discomfort. He never used an ice pack.

Franke [5] recommended ice packs secured to the bed post so that their weight would not lie on the eye. He suggested that a towel be placed between the bag and the skin if it was desired to reduce the action of the cold. Berens [7] strongly warned against direct application of ice to the eye because of its swift destructive effect on the epithelial circulation.

Gifford [8] described a practical method of applying cold used by Dr. Loyal Davis in neurosurgical cases at the Passavant Hospital, Chicago. A flexible bag was made of a thin rubber glove with tied-off fingers and filled with shaved ice. The bag was applied to the closed lids over a layer of gauze. No evidence of delayed healing or damaged corneal nutrition was observed, but the relief of pain and chemosis was often remarkable.

TEMPERATURE AND TISSUE CONDUCTIVITY

Von Michel [9] was the first investigator to measure the temperature and the tissue conductivity at different levels of the eyeballs of rabbits. He made the puncture to the desired depth with an atraumatic, needle-shaped electrode equipped with a thermometer; the opposite electrode was immersed in water at a constant temperature. As compared with the average body temperature of the rabbits (38.5 to 38.9 C. [101.3 to 102 F.]), the galvanometric reading for the center of the anterior chamber was 31.9 C. (89.42 F.) and that for the vitreous, 36.1 C. (97 F.). Results recorded by different authors vary within a limited range.[10] After studies with a similar apparatus, Giese [11] affirmed that, with 2 exceptions, each of a series of infected eyes displayed an elevation in temperature of the conjunctiva, the average temperatures for the conditions studied being as follows: blepharoconjunctivitis 36.07 C. (96.89 F.); catarrhal conjunctivitis 36.87 C. (98.3 F.); corneal infiltration, 36.49 C. (97.7 F.); trachoma without pannus, 36.43 C.

7. Berens, C.: The Eye and Its Diseases, Philadelphia, W. B. Saunders Company, 1936, p. 1014.

8. Gifford, S. R.: Physical Therapy in Ophthalmologic Practice, Arch. Ophth. **19**:171-180 (Feb.) 1938.

9. von Michel: Die Temperatur-Topographie des Auges, Arch. f. Ophth. **32**:227-232, 1886.

10. Comberg, W.: Auge und Allgemeinleiden; die physikalische Therapie, in Schieck, F., and Brückner, A.: Kurzes Handbuch der Ophthalmologie, Berlin, Julius Springer, 1932, vol. 7, p. 692.

11. Giese, R.: Temperaturmessungen in Conjunctivalsack des Menschen, Arch. f. Augenh. **28**:292-304, 1895.

(97.5 F.); acute iritis (1 case), 36.74 C. (98.15 F.), and panophthalmitis (3 cases), 36.56 C. (97.8 F.).

Application of iced compresses and ice bags to the eyes has been variously reported to cause a quick drop in the temperature of the conjunctiva of 1 to 15 degrees (C.) (1.8 to 27 degrees [F.]). Closing the lids brings a rapid rise of 2 to 3 degrees (C.) (3.6 to 5.4 degrees [F.]). According to Giese, the ice bag gave results inferior to those produced by direct application of cold compresses and was particularly ineffectual when separated from the eye by a strip of gutta-percha. The value of changing the compresses frequently was stressed by Hertel [12]; the optimal effect is obtained by replacement every thirty seconds. He asserted that his results were not influenced by diminished corneal circulation caused by the use of cocaine. Even compression of the carotid artery and subsequent anemia failed to reduce further the low temperature achieved by the use of ice water compresses. He therefore concluded that the thermoregulatory influence of the blood vessels during the application of hot or cold compresses is probably relatively small and that the action of the compresses is based not on changes in the state of the circulation but on conduction through the tissues. The response occurring in the deep layers he explained on the basis of the conductive power of the voluminous avascular eyeball. Iced compresses exerted a greater thermal effect than did hot compresses, and the action of cold was quicker and more lasting than that of heat.

METHODS OF APPLICATION

Hot Compresses.—In observing the application of compresses to the eyes by nurses or by patients, one is impressed with the difficulty encountered in a treatment which should be simple and which has a beneficial effect on so many pathologic conditions of the eye. After having patients experiment with various types of compresses, I have found the following procedure for application of heat to be simple, safe and productive of minimum discomfort to the patient and of maximum benefit to the eye.

Preparation of the compress is as follows:

A wooden spoon is obtained (fig. 1). This object forms a part of almost every household equipment or can be purchased in any five and ten cent store, in hardware shops and in some grocery stores. The bowl of the spoon is filled with cotton, and cotton also is applied to the back of the spoon. A 2 inch (5 cm.) gauze bandage is wrapped around the cotton in the form of a figure 8 and securely tied to prevent the cotton from falling out. Wide gauze can also be wrapped around the bowl and the cotton to form the compress. Hot water is poured into a small basin, and a medicament is added when prescribed. The compress is allowed to soak in the solution for a few minutes. It is then removed; the excess water is shaken off and it is applied to the eye (fig. 2). As wood is a nonconductor of heat, the spoon handle remains cool, and the compress is easily handled and adjusted. The patient is the best judge of the proper temperature. As soon as the compress begins to cool, the bowl of the spoon containing it is introduced again into the basin for reheating and is again applied to the eye.

Fig. 1.—Wooden spoon and compress made by placing cotton in the bowl and on the back of a spoon. A gauze bandage or layers of gauze are wrapped around the spoon and tied.

The duration and frequency of application are determined according to individual needs. Except with persons who are sensitive to heat or have a thin skin of the eyelids, application of a hot compress may be continued for fifteen minutes. The interval between applications de-

12. Hertel, E.: Wirkung von kalten und warmen Umschlägen auf die Temperatur des Auges, Arch. f. Ophth. **49**:125-167, 1899.

pends on the severity of the condition and the pain and discomfort associated with it. With severe disturbances, such as acute glaucoma and acute iridocyclitis, the compresses can be used every hour, and with milder ones, every three or four hours. A third consideration concerns the period over which application of the compress should be continued. This, again, depends on the type of the ophthalmic condition. In the case of a sty, it should be sustained until the sty points and is either opened or opens spontaneously and the inflammation has subsided; in cases of acute glaucoma and acute iridocyclitis, as long as pain persists and the condition of the eye demands. In cases of other conditions three or four days will suffice.

Fig. 2.—Spoon compress applied to the eye.

I have been able to find only two references to this method of treatment in the literature. The first reference is by Parsons,[13] who stated:

> Much better than the usual hot fomentations is the method of hot bathing used at Moorfields Eye Hospital. A pad of cotton wool is tied into the bowl of a wooden spoon. The wool is dipped into a bowl of boiling water, and is then approximated to the closed eye. As soon as it has cooled sufficiently it is brought into contact with the closed lids. As soon as it ceases to feel hot, the wool is again dipped in the hot water and the process repeated. The bathing is continued for ten to fifteen minutes, and then a pad of dry warm cotton wool is bandaged over the eye. The hot bathings may be repeated frequently.

The second is a statement by Duke-Elder.[14]

> It may be given as repeated bathings with hot water, which is most easily carried out with the aid of a wooden spoon carrying cotton wool.

Cold Compresses.—The simplest method of applying a cold compress is by placing cracked ice or ice cubes in a bowl of water. When the water is cold, cotton is dipped into the bowl, squeezed and applied to the eye. This can be repeated as soon as the cotton loses its frigidity. The procedure with the wooden spoon already described may also be employed. When ice is not available, tap water may be used. The water is allowed to run until cold. Cotton is held under the tap until a cold compress can be obtained and applied to the eye. As it is necessary to change the compress often, the tap water is allowed to run throughout the length of treatment.

Strips of gauze may be placed on ice cubes and then applied to the eyes.

An ice bag is sometimes recommended. This, as a rule, is not so satisfactory or efficient as a cold compress, because it is heavy and does not always properly cover the affected area.

COMMENT

Some patients obtain more relief from dry heat and others from moist heat, and it is occasionally a good plan to alternate the two. Certain patients seem to tolerate one form of thermal application better than the other, so that the decision whether to use heat or cold may often be determined largely by the patient's comfort.

SUMMARY

Heat and cold have been used in the treatment of ocular disorders from time immemorial.

Heat is a vasodilator, produces increased hyperemia and accelerates metabolism and leukocytosis. It is beneficial in the treatment of most inflammatory conditions, particularly of the anterior segment of the eyeball.

Cold is a vasoconstrictor, allaying pain and promoting healing by the production of anemia in the presence of chemosis and congestion.

My method of applying hot and cold compresses to the eye by means of moist cotton tied in the bowl of a wooden spoon with gauze has given gratifying results. The equipment is simple, safe and easily procurable.

The Columbia Foundation made this study possible.

490 Post Street.

13. Parsons, John H.: Diseases of the Eye, ed. 7, London, J. & A. Churchill, Ltd., 1934, p. 660.

14. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1941, vol. 3, p. 2210.

BILATERAL METASTATIC UVEITIS ENDING IN PHTHISIS BULBI AS A COMPLICATION OF MEASLES

REPORT OF A CASE

LOUIS C. RAVIN, M.D.

TOLEDO, OHIO

Ocular complications of measles, other than the almost invariably associated conjunctivitis, are rare.[1] Metastatic uveitis as a complication of measles was mentioned by Duke-Elder.[2] Optic neuritis,[3] retrobulbar neuritis with associated meningitis,[4] encephalitis with loss of vision [5] and severe retinitis [6] have also been reported as complications of measles.

REPORT OF A CASE

S. T., a 3 year old girl, was first seen on Dec. 18, 1943, for consultation, at the request of her physician. The child had been admitted to the hospital after a severe episode of measles with associated bilateral otitis media and pneumonia. Sulfathiazole therapy had been instituted three days previous to her admission. Ocular examination revealed moderate lacrimation and photophobia; the conjunctivas were hyperemic. The extraocular movements were well performed. A slight ciliary injection was evident in both eyes, but no keratic precipitates were noted grossly. Examination with a hand loupe and a slit lamp was unsatisfactory, owing to lack of cooperation. A slight turbidity of the aqueous could be detected. The pupils measured approximately 3 mm. in diameter. They were round and regular but did not react to light either directly or consensually. The irides lacked their normal luster. After instillation of atropine sulfate solution, complete, annular posterior synechias were noted in both eyes; there was a dense pupillary membrane, through which neither the lens nor the vitreous could be seen. The red reflex of the fundus could be detected around the periphery of the membrane. Ocular tension was normal to palpation with the fingers.

Drops of atropine sulfate solution were instilled every two hours, oral administration of sulfadiazine was ordered and dark glasses were put on. During the patient's four weeks' stay in the hospital the ciliary injection cleared and the photophobia subsided. The pupillary membrane became less dense. Some large floating opacities could be detected in the vitreous, but no details were discernible at any time. The fundus could not be seen. There was no perception of light with either eye. The vitreous gradually became opaque and finally developed into a pseudogliomatous mass.

The laboratory data revealed the following: The hemoglobin content was 11 Gm., the red blood cell count was 3,870,000 and the white cell count, 6,650. The urine contained no sugar or albumin, many bacteria and a rare white blood corpuscle. The blood level of sulfadiazine was maintained between 4.5 and 5 mg. per hundred cubic centimeters. A culture of the discharge from the external canal of the ear revealed gram-positive and gram-negative small rods.

The patient has been observed regularly since her discharge from the hospital. When last seen, on May 3, 1944, the vitreous was a large pseudogliomatous mass, through which the fundus could not be seen; the globes were soft and moderately shrunken. There was no perception of light with either eye.

1. Berens, C.; Kerby, C. E., and McKay, E. C.: Causes of Blindness in Children: Their Relation to Preventive Ophthalmology, J. A. M. A. **105**:1949 (Dec. 14) 1935.

2. Duke-Elder, S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1941, p. 2149.

3. Russo, A.: Optic Neuritis from Measles, Boll. d'ocul. **16**:276, 1937; abstracted, Am. J. Ophth. **21**:98, 1938.

4. Dabney, S. G.: Blindness Following Measles, Kentucky M. J. **30**:275, 1932.

5. Heath, P.: Measles Encephalitis, Am. J. Ophth. **15**:130, 1932.

6. Shlossberg, F. R., and Prizer, M.: Retinal Changes with Marked Impairment on Vision in Measles, Am. J. Ophth. **23**:998, 1940.

BINOCULAR ORTHOPTIC TRAINING FOR AMBLYOPIC PATIENTS

KENNETH C. SWAN, M.D.

PORTLAND, ORE.

AND

ELSIE LAUGHLIN

IOWA CITY

A review of the literature reveals that for many years visual acuity of 6/15 or 6/12 in both eyes has generally been accepted as a minimal requirement for orthoptic training. In view of recent developments in orthoptic methods and also because maximal visual acuity of 6/15 or less in one eye is common with neglected concomitant strabismus, reconsideration of the minimal visual acuity requirement is indicated.

Visual acuity of 6/15 or better is dependent on foveal function; however, persons with small central scotomas frequently have single binocular vision. Also it is generally accepted that the peripheral fields of vision play a predominant role in fusional movements. For these reasons no one doubts that singular binocular vision may exist without foveal function in one or both eyes. Rather, the premise that visual acuity of 6/15 or better is necessary for orthoptics seems based on the belief that foveal fixation is essential for accurate objective adjustment of orthoptic instruments and that complex stereoscopic targets containing fine details are always best suited for the development of fusional movements.

It is important to adjust the orthoptic instrument to correspond exactly to the deviation of the eyes, particularly in the treatment of anomalous retinal correspondence; otherwise, the targets will not be visualized by normally corresponding points on the two retinas. For this purpose the cover test is used almost universally; that is, the targets are shifted in position until no movement of the eyes is apparent when the patient alternates fixation. This method is often unsatisfactory even when the patient is capable of foveal fixation in each eye. In persons with convergent strabismus, and particularly in persons with overaction of an inferior oblique muscle, it is not rare for the deviation to vary 10 to 20 prism diopters, depending on which eye is fixating. For such patients it is impossible to adjust the instrument so that the eyes do not change position as fixation is alternated. For these patients and also for patients who are incapable of foveal fixation in one eye because of an absolute central scotoma, illuminated instruments such as the major amblyoscope are adjusted until the corneal reflexes are symmetric. In accuracy this method compares favorably with the cover test, providing the orthoptist accurately measures the angle gamma, the interpupillary distance and the distance of the eyes from the instrument. Therefore, it is not essential for the proper adjustments of instruments that both eyes be capable of foveal fixation.

Detailed targets exaggerating stereopsis stimulate fusional movements in patients with normal binocular vision, but in previously untreated squints the complexity and dissimilarity in the images of the two eyes are often confusing and favor alternation of fixation rather than fusion. Moreover, the fine details are not discerned by eyes with poor visual acuity. Targets consisting of simple colored disks subtending a visual angle of 1 to 3 degrees and lacking detailed points for foveal fixation are fused more readily. Patients with visual acuity as low as 6/60 in one eye are able to fuse these simple disk targets and acquire considerable amplitude of convergence and divergence provided that the extrafoveal fields of vision are relatively full and retinal correspondence is normal.

Development of single binocular vision is possible even when the patient has an absolute central scotoma in the afflicted eye, as is common in neglected monocular strabismus. In such patients with visual acuity of from 3/60 to 5/60 a large green ring with a central dot for fixation is presented to the normal eye, while a red ring with a blank background is presented to the amblyopic eye. To be visualized by the amblyopic eye the ring must subtend a visual angle larger than the scotoma.[1] Rings with a diameter

From the Department of Ophthalmology, College of Medicine, State University of Iowa, Iowa City, Iowa.

1. Red and green targets are projected on a white background, and filters are placed before the patient's eyes, so that he visualizes only the red target with one eye and only the green with the other eye. The scotoma is plotted with the better eye fixating.

subtending a visual angle of 5 degrees and with a rim wide enough to subtend an angle of 15 to 30 minutes suffice for most cases. The rings are colored to permit the patient to distinguish between the images of the two eyes. The colors are so balanced that the rings appear gray or black when fused but bright red and green otherwise. The illumination and contrast must be carefully controlled to minimize after-images and prevent retinal rivalry. Initially these targets are used with an instrument such as the major amblyoscope, which may be adjusted by the corneal reflex method to correspond to the deviation of the eyes, for it is imperative that the rings be visualized by normally corresponding retinal areas. When normal retinal correspondence is well established, rings printed on cards are used for home training with a simple prism stereoscope. With training many patients lacking sharp central vision in one eye fuse the rings and develop a considerable amplitude of fusional movements. Then single binocular vision becomes possible provided that the gross deviation of the eyes has been corrected by surgical intervention or by glasses.

When the better eye is occluded the squinting eye with an absolute central scotoma often fixates with an extramacular area, usually just adjacent to the nerve head. This point of eccentric fixation often has a visual direction corresponding to that of some point in the macular region of the usually fixating eye; that is, the patient has anomalous retinal correspondence. Until normal correspondence is established no attempt should be made to develop fusional movements by the use of ring targets. Rather, the ring targets should be used (repeated simultaneous stimulation of normally corresponding retinal areas) along with occlusion of the eccentrically fixating eye [2] to establish normal correspondence. This method of treatment has established peripheral fusion in only 20 per cent of our patients with eccentric monocular fixation, but it is probable that a higher percentage of successes will result as experience is gained. The establishment of peripheral fusion provides assurance that the deviation will be permanently corrected. Also, in several patients who had only peripheral fusion initially there has been some return of central vision in the amblyopic eye over periods of two to four years. Formerly only cosmetic surgical repair could be offered to these patients.

SUMMARY AND CONCLUSIONS

The generally prevalent concept that visual acuity of 6/15 or better is essential for orthoptic training is no longer applicable. It is desirable that each eye be capable of focal fixation so that the cover test may be utilized for the adjustment of orthoptic instruments; however, adjustment of illuminated instruments so that the corneal reflexes are symmetric provides an accurate alternative method which may be used when one eye lacks sharp central vision. In patients with poor visual acuity due to a central scotoma training must be directed toward peripheral fusion. For this purpose orthoptic targets containing many fine details are of little value, but simple disk and ring targets subtending visual angles larger than the central scotoma are applicable. The development of peripheral fusion assures the patient of a permanent correction of the deviation and in some instances of a partial return of central vision in the amblyopic eye.

2. Occlusion of the nonsquinting eye is harmful because eccentric fixation is stabilized by use. On the other hand, there is nothing to lose by occlusion of the squinting eye, for there is already an absolute scotoma which does not enlarge further.

TOPOGRAPHIC AND ETIOLOGIC STUDY OF 1,176 INDIGENT BLIND PERSONS IN MASSACHUSETTS

A BASIS FOR PREVENTION OF BLINDNESS

HUGO B. C. RIEMER, M.D.
BOSTON

In the past the census enumerator has been depended on to supply information as to the number of blind persons. The enumeration at its best has been incomplete and often incorrect. This was definitely proved in the National Health Survey conducted by the United States Public Health Service from 1935 to 1936.[1]

1. During the summer of 1930, the blind in a small Connecticut area were enumerated, one purpose being a comparison of results with those of the federal census. After thorough search it was found that not only was this special enumeration incomplete, but the Census Bureau had enumerated only 49 per cent of the blind in that area.

2. In the 1930 Census Bureau report, 626 blind persons were recorded for the State of Maine; yet in this State there were 1,268 persons receiving aid to the blind in April 1938, and it would not seem likely that all of the excess could be accounted for by difference in definition or by a real increase in the number of blind persons.

The census does not furnish authentic information as to the cause of blindness. This information, which is of utmost importance in the prevention of blindness, is now being obtained. The ophthalmologist considers a person blind when he no longer has perception of light, a condition known as amaurosis. The term blindness is now more inclusive. It includes that condition in which a person is considered to be economically blind, which actually means that he does not have sufficient sight for carrying on a gainful occupation.

Interest in the welfare of those handicapped by loss of vision has been greatly stimulated by the advent of the federal Social Security Act. This law was passed in 1935. In accordance with it the federal government makes provision for indigent blind persons by paying to the participating state one half of all payments up to $40 a month. That is, if the state grants a person $40 a month the federal government reimburses one half, or $20. The state, by accepting the benefits of the provisions of this law, actually becomes a co-partner of the federal government in its operation. Since the federal government has assumed a part of the responsibility, it naturally follows that it will participate in carrying out the provisions of this law.

The federal government has promulgated certain regulations in order to make the law more universally applicable to all the states and to see that provision is made for equitable treatment and distribution of funds to all applicants for and recipients of financial assistance.

In order to facilitate its operation, the Social Security Board soon after the act became operable made certain definite recommendations relative to blindness:

1. It proposed a definition of economic blindness.

2. It required that certain medical data be collected and that they be kept by the state agency for each applicant for assistance, and, further, it suggested that the medical examination be made *only* by an ophthalmologist who holds a certificate from the American Board of Ophthalmology. This enables the state to have an authentic record of each person who applies for aid to the blind.

3. It developed a form of medical record covering certain medical data to be filled out by the ophthalmologist after his examination. Massachusetts used the suggested form until recently, when the Medical Advisory Committee and the director of the Division of the Blind composed a new form, which includes all the requirements set up by the Social Security Board but is developed in a way that best meets the need in Massachusetts. This form requires an accurate description of each eye and a statement as to the primary cause of blindness. The cause of blindness eventually will furnish authentic data, which can be used as the basis of a real program of prevention.

4. The board suggested the appointment of a trained ophthalmologist to review all medical reports.

Many of the states have appointed ophthalmologists to supervise their medical activities. It is the duty of the supervising ophthalmologist to review the medical report of each applicant

1. National Health Survey 1935-1936, Bulletin 10, United States Treasury Department, Public Health Service, 1938.

for relief because of blindness. If the report is incomplete or unsatisfactory a reexamination is required. When there is a doubt in the mind of the supervising ophthalmologist as to the facts reported, he can request that the applicant appear before him for examination. In some states medical reports on all blind persons requesting any type of service from the state department are required. In the state of New York medical forms for all blind persons who may become known to any public welfare department are filed with the Commission for the Blind. These are catalogued so that from this file studies of any one cause of blindness can be initiated.

Reliable statistics as to the prevalence of blindness are now being obtained. This has been accomplished by insisting on proper medical reports, as initiated by the Social Security Board. Even though these statistics represent only the number of needy blind persons, a truer picture of the causes of blindness in this country will be secured. One may even hope in a few years to obtain adequate information concerning the incidence of blindness.

The Massachusetts Division of the Blind, which is concerned chiefly with education and rehabilitation of blind persons and with the care of indigent blind persons, is now greatly concerned with a larger and more important program—prevention of blindness for all residents of Massachusetts.

This prevention of blindness program needs the full cooperation of all the members of the medical profession. This responsibility rests on them as well as with the ophthalmologists. How well physicians carry out the provisions of the laws which aim primarily to prevent blindness will be one of the most important factors in the prevention of blindness.

No one will argue that the use of prophylactic drops in the eyes of newborn infants has not reduced the incidence of blindness from ophthalmia neonatorum. Statistics have proved without a shadow of a doubt that this is true. Within the past year not a single baby who was blinded because of this disease has been reported to the Massachusetts Division of the Blind. It becomes more important than ever to be vigilant in cases of childbirth, since it is a well known fact that the incidence of venereal diseases increases in wartime. The law in Massachusetts requires a Wassermann or a Hinton test of pregnant women and provides for treatment of syphilis when present in the early stages of pregnancy, not only to benefit the mother but to prevent the birth of syphilitic offspring, who may later acquire interstitial keratitis, one of the important causes of blindness.

The law requiring a Wassermann or a Hinton test before marriage in Massachusetts has the same aim—to prevent syphilitic offspring, who may later become blind.

When it is realized that communicable diseases and trauma are two of the most important causes of blindness, I believe that there is complete agreement that something can be done to reduce the number of persons whose blindness is caused by one of these factors.

It is of interest to note that committees on conservation of vision have been appointed by state medical societies in the following states: Alabama, Connecticut, Florida, Indiana, Kansas, Maine, Missouri, Nebraska, New Hampshire, New Jersey, Oklahoma, Oregon, Pennsylvania, South Carolina and West Virginia. Special committees, concerned also with conservation of vision have been appointed by state medical societies in the following states: Delaware, Georgia, Iowa, Minnesota, New Hampshire, South Dakota, Tennessee and Wisconsin.

Plans are also under way for the publication of an article in the *West Virginial State Medical Journal* which will discuss (1) industrial accidents, (2) glaucoma, (3) ophthalmia neonatorum and (4) trachoma.

Data on the cases of 1,176 blind persons receiving aid for the blind in Massachusetts have been coded in accordance with the standard classification developed by the Committee on Statistics of the Blind. Table 1 gives these data on the basis of topography and type of disease.

It is interesting to note that of diseases which involve the eyeball glaucoma heads the list, with 111 cases, and myopia is second, with 100. In 38 cases blindness was caused by structural anomalies, such as albinism, anophthalmos, megalophthalmos, aniridia, coloboma and multiple structural anomalies.

In 187 cases blindness was due to disease involving the cornea, and in 114 of these it was due to ulcerative keratitis.

There were 100 cases in which blindness was caused by diseases of the iris and the ciliary body; in 78 of these it was due to iridocyclitis and uveitis and in 18 to sympathetic ophthalmia.

Disease involving the crystalline lens was responsible for blindness in 181 cases, not an unusually large number considering the age of the persons affected.

There were 217 cases in which involvement of the choroid and retina was responsible; in 60 of these the blindness was due to chorioretinitis, in 59 to retinal degeneration, in 37 to retinal hemorrhage, in 29 to arteriosclerotic disease and in 25 to separated retina.

TABLE 1.—*Classification of Blindness on the Basis of Topography and Type of Disease*

	No. of Cases		Per Cent
Eyeball in general		275	24
Hypertension (glaucoma)	111		9.5
Refractive error (myopia)	100		8.5
Panophthalmitis and acute endophthalmitis	16		1.3
Structural anomalies	38		3.3
Degenerative changes	6		
Diseases of eyeball	4		
Cornea		187	16
Keratitis, interstitial	16		1.3
Keratitis, phlyctenular	1		
Keratitis, ulcerative	114		9.6
Pannus	10		0.9
Ulceration and vascularization	23		2
Other diseases of cornea	23		2
Iris and ciliary body		100	8.5
Iritis	1		
Iridocyclitis and uveitis	78		6.5
Keratoiritis	3		
Sympathetic ophthalmia	18		1.5
Crystalline lens		181	15
Cataract	179		15
Dislocated lens	2		
Choroid and retina		217	18
Choroiditis	3		
Retinitis	1		
Chorioretinitis	60		5
Detached retina	25		2
Retinal hemorrhage	37		3.3
Retinal degeneration	59		5
Arteriosclerotic disease of choroid and retina	29		2.5
Other diseases of choroid	3		
Optic nerve, visual pathway and cortical visual centers		205	17
Optic nerve atrophy	145		12
Optic neuritis	14		1.2
Papilledema	5		
Neuroretinitis	4		
Retrobulbar and intracranial lesions	33		2.7
Other diseases	4		
Miscellaneous and ill defined regions		11	1
Amblyopia, undefined	11		1

TABLE 2.—*Etiologic Classification of Blindness*

	No. of Cases		Per Cent
Infectious diseases		376	32
Measles	1		
Meningitis	7		
Ophthalmia neonatorum	51		4.3
Gonorrheal	32		2.7
Type not specified	19		1.5
Scarlet fever	3		
Septicemia	5		
Syphilis	128		10
Prenatal	22		2
Acquired after birth	101		8.5
Origin not specified	5		
Trachoma	14		1.2
Tuberculosis	12		1
Other infectious diseases, specified	5		
Infectious disease, not specified	150		12.8
Trauma (including chemical burns)		61	5.2
Nonoccupational activities	25		2
Occupational activities	25		2
Activities, not specified	11		1
Poisoning		13	1.1
Neoplasm		18	1.5
General diseases (not elsewhere classified)		93	7.9
Diabetes	45		3.8
Vascular diseases	40		3.4
All others	8		
Diseases of prenatal origin (not elsewhere classified)		152	13
Of hereditary origin, established	5		
Of hereditary origin, presumed	141		12
Of prenatal origin, cause not specified	6		
Cause undetermined or not specified		463	39
Unknown to science	348		30
Undetermined by physician	77		6.5
Not specified	38		3.3

Blindness was caused by disease involving the optic nerve and the visual pathway in 205 cases; in 144 of these it was due to atrophy of the optic nerve and in 33 to retrobulbar and intracranial lesions.

Table 2 classifies the causes of blindness.

Under infectious disease there are 376 cases, slightly over 31 per cent. In 128 cases (about 11 per cent of the whole number) blindness was due to syphilis, and in 101 of these it was due to syphilis acquired after birth. In 51 cases (about 4.5 per cent) it was caused by ophthalmia neonatorum; in 32 of these the ophthalmia was due to gonorrhea. One hundred and fifty cases (almost 13 per cent) are classified under infectious diseases with the cause not specified.

TABLE 3.—*Age at Onset of Blindness*

	No. of Persons in Age Groups	Per Cent of Total
Total for all ages	1,176	100.0
At birth	98	8.3
Under 1 year but not "premature" or "at birth"	46	3.9
1 year and under 10 years	124	10.5
10 years and under 20 years	75	6.4
20 years and under 30 years	96	8.2
30 years and under 40 years	139	11.8
40 years and under 50 years	190	16.2
50 years and under 60 years	186	15.7
60 years and under 70 years	129	11.0
70 years and under 80 years	58	4.9
80 years and over	16	1.4
Unknown	19	1.6

In 61 cases blindness was caused by trauma, including chemical burns. In 25 of these it was due to nonoccupational activities and in 25 to occupational activities.

In 13 cases blindness was due to poisonings and in 18 to neoplasms.

Under general diseases there are 93 cases; in 45 of these the blindness was due to diabetes and in 40 to vascular disease.

In 152 cases (practically 13 per cent) blindness was due to conditions of prenatal origin. In 141 it was caused by retinitis pigmentosa of presumed hereditary origin. In 5 cases the hereditary origin was established.

The cause was undetermined or not specified in 463 cases, or practically 40 per cent. In 348 cases (nearly 30 per cent), including cases of myopia, cataract and glaucoma, the cause was unknown to science. In 77 cases the cause was not determined by a physician.

Table 3 gives the age at the onset of blindness. The largest number of persons, 186, or about 16 per cent, became blind between 50 and 60 years of age, and the next largest number, 139,

or about 12 per cent, between 30 and 40 years of age. There were 124, or 11 per cent, from 1 to 10 years of age. Ninety-nine persons had been blind since birth. The decrease in the number of persons between 70 and 80 years of age really begins with persons at the age of 65, when many recipients of aid prefer old age assistance to assistance because of blindness.

It has been shown by this statistical study that the causes of blindness in percentages correspond closely to those in other states in which a similar study has been made.

Brewster, of New Orleans, in a similar statistical study of 700 blind persons, made the optimistic statement that in 73 per cent of these persons blindness could have been prevented.[2] His statistics as to the percentage of the various causes of blindness correspond closely to mine.

A survey [3] in Indiana of 2,551 blind persons up to June 1938 gives as the causes of blindness

Infectious diseases	30.1%
Trachoma	9.6%
Syphilis	7.5%
Injuries	8.4%
Congenital and hereditary	8.3%
Noninfectious systemic diseases	7.4%

The director of the Division of the Blind in Massachusetts, with the cooperation of the Medical Advisory Committee, has had the following laws enacted in Massachusetts, which became effective in 1943.

First, an act relative to recording the treatment of infants at birth. This law requires the physician or a medical officer of the hospital to treat the eyes of an infant within two hours after birth with a prophylactic remedy furnished or approved by the Department of Health and to record on the birth certificate the use of such a prophylactic. Whoever violates this section shall be punished by a fine of not more than $100. The principal change which this new law makes is that it requires the attending physician to record the use of the prophylactic on the birth certificate. Permissive legislation became effective in 1910, when the state furnished the prophylactic drops. The use of prophylactic drops was made mandatory in 1936.

Second, an act relative to reports of the treatment of certain wounds. This act classifies wounds caused by B. B. guns or other air rifles with the firearm or gunshot wounds which must be reported to the Commissioner of Public Safety or to the police authorities of the town.

Third, a law making it mandatory to report all cases in which vision is 20/200 or less in the better eye or the peripheral field of vision has contracted to a radius of 10 degrees or less, regardless of visual acuity.

Prevention of blindness should be the chief interest of all official agencies for the blind and every other agency concerned with the welfare and the health of all persons. This program for prevention of blindness cannot succeed without the full cooperation of the entire medical profession. There are certain fundamentals on which such preventive measures must rest. These fundamentals are:

1. Adequate medical determination of blindness.

2. Early contact with potentially blind persons.

3. Ability to care for those who are potentially blind, whether adults or children in an adequate manner.

4. Proper prenatal care.

5. Proper liaison between official agencies for blind persons and other agencies, such as the health department, the public safety department, industrial commissions, labor commissions and the education department.

Statistical studies of the causes of blindness form the basis of any real program of prevention. A broad program for the prevention of blindness requires the cooperation of local communities, philanthropic societies and physicians. When the causes are known, efforts at prevention can begin.

This study emphasizes the following needs:

1. Enforcement of all laws enacted for the control of infectious diseases.

2. More care in reporting the cause of blindness.

3. Early detection of all cases of glaucoma.

4. Detection of diabetes before the devastating effects of this disease are manifest.

5. Prevention of industrial and nonindustrial injuries.

6. Authentic data on cases in which blindness is hereditary.

7. Adequate measures to assure proper medical care for persons afflicted with disease or injury to prevent onset of blindness.

A new bill, the Barden-Lafollette Bill, Public Law 113, effective since July 6, 1943, aims to provide measures to rehabilitate all persons who are blind because of industrial injuries and others who can be restored by physical or medical means to a self-supporting status. These include blind persons in whom sufficient sight might be restored to allow a gainful occupation.

2. Brewster, H. F.: Causes of Blindness in Louisiana, New Orleans M. & S. J. **91**:166-173 (Oct.) 1938.

3. Kettler, J. R., and McCaslin, J. R.: State and the Blind, J. Indiana M. A. **31**:539-543 (Oct.) 1938.

Ophthalmologic Reviews

EDITED BY DR. FRANCIS HEED ADLER

EPIDEMIC KERATOCONJUNCTIVITIS AND VIRUS DISEASES OF THE EYE

ANDREW RADOS, M.D.

NEWARK, N. J.

VIRUS DISEASES WITH OCULAR COMPLICATIONS

Virus diseases and the closely related rickettsial infections may involve the eye secondarily. The complications of the virus group of diseases are so well known that it will suffice here merely to mention the varieties that may commonly affect the eye, such as measles, rubella, rabies, psittacosis, the common cold, influenza, encephalitis, lymphocytic choriomeningitis, poliomyelitis, Australian X type of encephalitis, louping ill, Rift Valley fever (enzootic hepatitis), yellow fever, pappatacci fever, dengue, vaccinia, mumps and lymphogranuloma venereum.

Rare and Recent Forms.—In rare instances virus diseases affecting animals only may produce ocular complications in human beings. Babel [1] described a serofibrinous iritis accompanying pseudotyphus meningitis (swineherd's disease) and cited Fatzer, who noted papillitis as a complication in his case. In Babel's case cultures of the aqueous inoculated into the anterior chamber of the eye of the rat, mouse and guinea pig gave negative results.

One of the diseases with which ophthalmic symptoms most commonly occur is encephalitis. The ocular complications of encephalitis were analyzed by Kennedy [2] as due either to obliteration of normal function or to release of functions normally controlled by centers higher in the brain. The most usual complications were ptosis with associated weakness, paralysis of both external rectus muscles, combined paresis of the third and sixth nerves, divergence paralysis and blepharospasm, due to the downpouring of tonic impulses from the basal ganglions when freed of their normal cortical control.

Paralysis of the external rectus muscles is caused by the perivascular lymphocytic infiltration of the brain stem around the aqueduct. A lesion of the quadrigeminal plate manifests itself in the Parinaud syndrome, diminution or loss of vertical conjugate movements or interference with lateral conjugate action. Inequality of the pupils appears temporarily, with the Argyll Robertson phenomenon, usually bilateral paralysis of accommodation and various types of nystagmus, indicating involvement of Deiters' nucleus or the central vestibular connections. Furthermore, retrobulbar neuritis and papilledema may be produced by their widespread neurotrophic infection.

In the more recent, and generally less known, literature it is worth while to note the complications of mumps. Danielson and Long [3] referred to 7 instances of unilateral keratitis, in addition to their own cases. Dacryoadenitis, scleritis, uveitis, retrobulbar neuritis, neuroretinitis and ocular palsies are known to be associated with epidemic parotitis. Packard [4] called attention to corneal involvement in cases of varicella and referred to a similar observation by Oppenheimer.

In his review, Bruce [5] gave a fair picture of ocular complications associated with the common virus diseases. Only lymphogranuloma venereum merits special mention, having been described as recently as 1913 by Durand, Nicolas and Favre. The diagnosis of lymphogranuloma venereum was greatly facilitated by the specific cutaneous test of Frei. Von Haam and Hartwell [6] observed unilateral or bilateral conjunctivitis following intracerebral inoculation of the virus in mice,

Read at a meeting of the Academy of Medicine of Northern New Jersey, Section of Diseases of the Eye, Ear, Nose and Throat, Newark, N. J., Oct. 11, 1943.

1. Babel, J.: Fibrinous Iritis in Patient with Swineherd Disease, Ophthalmologica **96**:159, 1938.

2. Kennedy, F.: Ocular Disturbance in Epidemic Encephalitis, J. Nerv. & Ment. Dis. **69**:194, 1929.

3. Danielson, R. W., and Long, J. C.: Keratitis Due to Mumps, Am. J. Ophth. **24**:655, 1941.

4. Packard, R.: Varicella of the Cornea, Brit. J. Ophth. **20**:15, 1936.

5. Bruce, G. M.: Virus Diseases and the Eye in Childhood, J. Pediat. **18**:592, 1941.

6. Von Haam, E., and Hartwell, R.: Experimental Conjunctivitis Caused by Virus of Lymphogranuloma Inguinale, J. Trop. Med. **39**:190, 1936.

monkeys, ferrets, cats, sheep and calves. The development of a lesion was a positive sign of infection and was followed by fatal meningoencephalitis. These authors observed only acute hemorrhagic or purulent conjunctivitis in cases of lymphogranuloma venereum. Weimer and his associates [7] presented the case of a Negro aged 32 with a lesion of the left upper lid, the site of an extragenital infection associated with lymphogranuloma venereum. Histologic study revealed large monocytes containing Donovan bodies.

Levaditi and his co-workers [8] described a case of the Parinaud syndrome with preauricular and submaxillary adenopathy. This observation was confirmed by the findings of Hashimoto and Tamata [9] in 3 cases and by the convincing description of the disease by Appelmans,[10] who followed the development of the Parinaud syndrome in a young woman, a laboratory worker. She had accidentally acquired the infection while working with the virus. In Meyer and Reber's [11] case the virus origin of a superficial, narrow, crescentic corneal ulcer in a patient with lymphogranuloma venereum of the rectum is questionable, for biopsy of the lesion or recovery of the virus, with confirmatory inoculation, was lacking.

An entirely new chapter in the knowledge of sequelae to virus diseases was opened by the observations of Gregg [12] and Swan and co-workers [13] on congenital abnormalities in infants whose mothers had contracted rubella while pregnant. This work is so recent that all the possible consequences of the infection cannot as yet be fully ascertained.

The first observation was furnished by Gregg, who described the cases of 78 infants with congenital cataract (62 with bilateral and 16 with the unilateral type) whose mothers, with few exceptions, had had rubella in the early part of pregnancy. Forty-four infants simultaneously had a congenital lesion of the heart. The cataracts were of the dense nuclear variety. Eleven of the infants with monocular cataract had microphthalmia. Gregg emphasized that these cataracts had no similarity to any of the morphologic types of congenital and developmental opacities previously reported.

Based on the reports of Gregg, Swan and his associates made an exhaustive study of 49 women with rubella to whom 31 infants were born with congenital abnormalities. Of these 49 women, 35 were examined while they had the eruption; the remaining 14 (with 13 congenitally defective infants) failed to seek medical advice at the time of the alleged rash, and hence the clinical diagnosis could not be confirmed by medical examination. All but 2 of the 31 mothers with congenitally defective infants had rubella within the first three months of pregnancy. All the 25 patients who had rubella in the first two months of pregnancy gave birth to infants with congenital abnormalities. Of 8 women who had rubella in the third month of pregnancy, only 4 gave birth to defective offspring.

Of 14 infants with defective eyes, 13 (6 males and 7 females) had cataracts and 1 (a female) buphthalmos. With 2 exceptions, none of the mothers had been pregnant more than two months at the time of onset of the exanthem. Of the infants with cataract, 10 had bilateral and 3 unilateral involvement, and all the cataracts were of the central nuclear type. Two of the infants had nystagmus, 1, moderately sever microphthalmia, and another microphakia. One of the infants with bilateral cataract presented microphthalmia in one eye and small pigmented spots in the fundus of the other eye. The clinical appearance of the cataracts conformed to Gregg's description—a flattened, white, dense disk with six radiating lines, the latter presumably representing the superimposed anterior and posterior sutures. The lens appeared to be small, and in good mydriasis a clear peripheral zone was noted. On discission, the capsule and the cataractous disk seemed to be adherent. Nine of the infants showed cardiac involvement; 3 mental deficiency, and 1, talipes equinovarus.

Of the infants with no involvement of the eyes, 7 were deaf-mutes, and 17 had cardiac lesions and microcephaly.

For the mothers whose infants had cataract, the average duration of pregnancy at the time of the appearance of the exanthem was one and a half months, while for the mothers of the deaf-mute children it was two and one-tenth months,

7. Weimer, A. L.; Gaynon, I. E., and Osherwitz, M. S.: Granuloma Inguinale of Eyelid: Report of Case, Am. J. Ophth. **26**:13, 1943.

8. Levaditi, C.; Bollack, J.; Basch, G., and Desvignes: Conjunctivitis with Adenopathy, Due to Virus of Nicolas-Favre's Disease, Bull. Soc. franç. de dermat. et syph. **43**:1238, 1936.

9. Hashimoto and Tamata: Poradenic Etiology of Parinaud's Conjunctivitis, Sang **12**:85, 1938.

10. Appelmans: Parinaud's Conjunctivitis Caused by Virus of Nicolas Favre's Disease, Bull. Soc. belge d'opht., 1938, no. 77, p. 130; Ophthalmologica **96**:321, 1938.

11. Meyer, G. P., and Reber, J.: A Case of Corneal Ulcer Associated with Lymphogranuloma Venereum, Am. J. Ophth. **24**:161, 1941.

12. Gregg, M. N.: Congenital Cataract Following German Measles in the Mother, Tr. Ophth. Soc. Australia **3**:35, 1941.

13. Swan, C.; Tostevin, A. L.; Moore, B.; Mayo, H., and Black, G. H.: Congenital Defects in Infants Following Infectious Diseases During Pregnancy, M. J. Australia **2**:201, 1943.

evidence that the type of congenital defect is dependent on the stage of pregnancy at which the rubella occurs.

The unusually large number of congenital defects following rubella in this series may have been due to an altered virulence of the virus. The embryonic cells are more susceptible to infectious agents than those of adult tissues. The young and the outgrown tissues are known to differ biologically in behavior toward certain agents. In this connection I should like to note that the lenses of young rabbits are more sensitive to irradiation than those of adult rabbits; consequently, a smaller dose will produce radiation cataracts. Furthermore, the same agent, radiation, produces retinal rosettes in the embryonic rabbit if the pregnant uterus is exposed to roentgen rays. In cases of rubella the virus penetrates the chorionic barrier and produces severe lesions in the embryonal tissues. It appears that the cells are highly susceptible only in the first three months of pregnancy, or it may be that after that period, the placenta being formed, the barrier between mother and fetus becomes impenetrable to the offending virus.

OCULAR COMPLICATIONS IN RICKETTSIAL INFECTION

The ocular complications of rickettsial disease were recently reviewed by Venable and Pollock.[14] These diseases are all insect borne and show the Weil-Felix reaction with Proteus X19 or Proteus XK; they usually confer long-lasting immunity. The rickettsias are minute bacillary or diplobacillary organisms. Like the viruses, the pathogenic rickettsias multiply outside the body only, in various kinds of tissue cultures, and develop intracellularly. The organism of typhus lies in the cytoplasm, and that of Rocky Mountain spotted fever often grows intranuclearly in tissue cultures. They show apparent selective affinity for certain types of cells. Though the rickettsias occur in all organs and in the blood, they accumulate visibly in cells of mesothelial origin, particularly in the lining cells of the large serous cavities of the body. The frequency of the presence of ricksettsias in insects and their growth in tissue cultures at a temperature lower than that of the mammalian body suggest that they originally were insect parasites. Their characteristics of nonfiltrability, visibility and affinity for ordinary bacterial stains ally them with bacteria. In their staining reactions with special methods (Giemsa, Castenada and Machiavello), their growth in living cultures and their intracellular position, as well as their affinity for mesothelial cells, the rickettsias show points in common with the viruses.

According to Pinkerton, the rickettsias are pleomorphic bacteria adapted to anthropod tissues. At present, they are considered to belong to an intermediate class between viruses and bacteria. They may eventually be included with the bacteria. Typhus (Rickettsia prowazeki) is transmitted by the louse or flea; Rocky Mountain spotted fever (Rickettsia dermacentroxenus), by ticks. In contrast to these diseases, boutonneuse fever and tsutsugamushi fever are similar in that there are local ulceration and adenopathy at the site of the tick bite. Trench fever, proved to be transmitted through the louse, is most probably also a rickettsial disease. Ocular complications are observed with typhus. Only mild conjunctivitis occurs with Rocky Mountain spotted fever. In cases of tsutsugamushi fever Nagayo and associates[15] observed severe inflammatory complications in the anterior segment of the eye. He produced the lesions by introducing infected material into the anterior chamber of the eye in rabbits, monkeys and guinea pigs. The infected eye acquired lasting immunity, and the endothelial cells of Descemet's membrane exhibited a large number of rickettsias.

CHARACTERISTICS OF VIRUSES

The genius of Pasteur anticipated that rabies is caused by an invisible organism smaller than bacteria, but the actual proof was furnished in 1892 through the transmission of the mosaic disease of the tobacco plant by cell-free filtrates (Swanovski and Beijerinck). The existence of such filtrable organisms was shortly confirmed by evidence that foot and mouth disease is similarly caused by invisible agents. The last two decades have brought an enormous amount of knowledge concerning the propensities of the agent, and numerous diseases belonging to the virus group have been discovered.

With the resolving power of the ordinary microscope and with the usual illumination the viruses in general are invisible. They pass through the pores of porcelain filters or collodion membranes of determinable porosity and are grown only in cultures of living tissues. Their cultivation in the presence of living, susceptible cells indicates their intimate relation to the host cell. The various viruses often adapt themselves to one or to a few animal or plant hosts or are

14. Venable, H. P., and Pollock, F. J.: Rickettsias in Ophthalmology, Arch. Ophth. **30**:362 (Sept.) 1943.

15. Nagayo, M., and others: Rickettsia Orientalis as Causative Agent of Tsutsugamushi Disease, Jap. J. Exper. Med. **9**:87, 1931; Virus of Tsutsugamushi Fever, Compt. rend. Soc. de biol. **104**:637, 1930.

characterized by special affinity for a group of cells in the host, such as that of the herpes virus for ectodermal derivates. The invaded cellular elements react typically to the virus with stimulation or destruction or with the formation of inclusion bodies. Immunity is often lasting (variola, varicella) but may be either transient (herpes simplex, common cold) or not demonstrable (trachoma, molluscum contagiosum).

A description of the exact nature of the viruses is unnecessary, in view of the excellent review by Thygeson.[16] It should be mentioned that the viruses show enormous range in size, even after one discounts the possible error in measuring the particles on which the virus was adsorbed. The scale varies from 150 or 250 millimicrons (in vaccinia and psittacosis) to 10 to 12 millimicrons (in poliomyelitis and aphthous stomatitis [foot and mouth disease]).

Through animal passage the properties of a virus may change, and adaptation occurs, resulting, for instance, in conversion of the smallpox virus into the vaccinia virus or into the yellow fever virus, with production of encephalitis in monkeys. The cell reacts to invasion of the virus with the formation of cytoplasmic or nuclear inclusions. Some of the inclusion bodies are characteristic enough (Negri bodies in rabies, and the bodies in molluscum contagiosum) to permit microscopic diagnosis of the disease in question. Their exact nature is still debated, but doubtless they express the influence of the virus on the cell. The inclusion bodies were regarded as indicating reactive inflammation or degeneration of the cell, or as being aggregates of the virus itself or particles of the virus enveloped by cellular material. The last concept led von Prowazek to designate them as chlamydozoa, or mantle animals. The inclusion bodies are not necessarily present in every virus disease; they are absent, for instance, in poliomyelitis. These bodies, being larger than the virus, necessarily contain cellular material too. Von Prowazek and Lipschütz,[17] the latter using the designation strongyloplasm, concluded that the inclusion body was a microcolony of the virus. Lipschütz observed even brownian movements. The most recent investigations with microdissection of the inclusion, in which the body is dissolved by means of an alkaline solution of trypsin, seem to furnish further evidence of a hyaline-like matrix and minute particles. The matrix is the product of the cell reaction and varies in chemical constitution with the specific virus.

Serum obtained from patients after recovery from the disease neutralizes the homologous virus. The presence of complement fixation, precipitation and agglutination antibodies testifies to the active antigenic nature of the viruses, with specific properties. The presence of virus-neutralizing antibodies is utilized in neutralization tests for diagnostic purposes. The serum, after being mixed with the virus, is inoculated into susceptible animals. The presence of complement fixation antibodies in convalescent serums is one of the most conclusive evidences of the presence of the virus, especially since these antibodies are absent in the acute stage. The neutralization tests are of great diagnostic significance in cases of such diseases as encephalitis, poliomyelitis, psittacosis, herpes and epidemic keratoconjunctivitis. The neutralizing antibody test, however, has limitations, since a typical attack may fail to develop, or, on the other hand, the disease may occur in persons already possessing antibodies in their serum.

The exact nature of the viruses is still debated. A bacterial origin is generally considered improbable. According to the fundamental attributes of life, namely, reproduction and adaptation, the viruses are living organisms. They have antigenic properties and show the faculty of adaptation in response to different environments. But all these properties are linked by the association of the virus with living cells, either in the body of the host or in cultures containing living cells. Actual proof of the living nature of viruses—cultivation without the presence of living cells—has not been obtained.

Many investigators consider the viruses as autocatalytic, enzyme-like agents and believe that their minute size, for example that of the virus of poliomyelitis, as shown by differential filtration and ultracentrifugation, precludes the possibility of their being living things. The discovery by Stanley of the crystalline form of the virus of tobacco mosaic disease, confirmed by other investigators, seems to prove that viruses are not animate organisms. But in Pirie's opinion, crystallinity denotes a structural regularity only, and not incompatibility to a living state.

The enormous progress in the study of virus disease in the past two decades has taught that demonstration and identification may be accomplished by the use of susceptible animals and chick embryos. After the virus is recovered, it is identified by determination of the susceptible

16. Thygeson, P.: Viruses and Virus Diseases of the Eye, Arch. Ophth. **29**:285 (Feb.); 488 (March); 635 (April) 1943.

17. Lipschütz, B.: Further Contributions to Knowledge of Molluscum Contagiosum, Arch. f. Dermat. u. Syph. **107**:387, 1911.

animal, the routes by which it can be introduced into the animal and the specific immunologic reaction, the last being extremely useful in differentiation of viruses producing apparently identical lesions. The complement fixation reaction proved to be reliable when infected tissues were used as antigen. The best results are obtained by incubation at a low temperature for several hours —the optimal condition for the union of antigen and antibody. Precipitation or flocculation reactions are less reliable. One of the important methods for isolation, cultivation and titration of the viruses and antiviral serums and for study of the local lesions produced by the inoculation was developed in the employment of the chick embryo. Storage of viruses at low temperature gave evidence that they are unstable, become rapidly inactivated at room temperature and can be kept indefinitely and still retain their infectivity. Improvement in methods is largely responsible for the advance in the diagnosis and differentiation of viruses which morphologically are almost identical.

Sulkin and Harford [18] have tabulated the essential items concerned with the laboratory diagnosis of virus diseases in man. In view of the usefulness and accuracy of the table, the section on laboratory diagnosis of the virus infections of the eye is summarized:

1. Herpes: Detection of the virus on the skin and genitalia; neutralization tests, and study of the histopathologic changes and inclusions. The laboratory test of choice is inoculation of the rabbit. Direct inoculation of the chorioallantoic membrane of the developing chick embryo with fluid from a herpetic lesion is a useful procedure.

2. Herpes zoster: Study of the histopathologic changes and inclusion bodies and biopsy.

3. Trachoma and inclusion conjunctivitis: Detection of virus in the conjunctiva and in the genitalia in the latter disorder as well; histopathologic examination and study of the inclusions, and smears. In the diagnosis of trachoma the monkey is the animal of choice for transmission of the disease.

4. Epidemic keratoconjunctivitis: Detection of the virus in the conjunctiva, the neutralizing test, histopathologic examination and inoculation of the mouse.

5. Verruca vulgaris and molluscum contagiosum: Histopathologic examination, study of the inclusions and biopsy.

18. Sulkin, S. E., and Harford, C. G.: The Laboratory Diagnosis of Virus Diseases, J. A. M. A. **122**: 643 (July 3) 1943.

EPIDEMIC KERATOCONJUNCTIVITIS

The first epidemic of keratoconjunctivitis recorded in the literature appeared in 1889 in Vienna (Weiss [19] erroneously gave the date as 1893) and was reported by Adler,[20] von Reuss [21] and Fuchs [22] in the same year and by von Stellwag in 1890.[23]. The observations, descriptions and morphologic designations of the first epidemic by these four authors showed discrepancies and, accordingly, led to different designations of the disease. Fuchs described the disease as keratitis punctata superficialis; Adler, as keratitis subepithelialis; von Reuss, as keratitis maculosa, and von Stellwag, as keratitis nummularis.

In his paper, Fuchs [22a] reported his experience in the observation of 36 cases; he described the disease as keratitis punctata superficialis in the first edition of his textbook [22b] and therefore felt he should retain the same term in his paper. With classic clarity, he noted the clinical propensities and the possible etiologic classification of the disease. According to Fuchs, the corneal lesion is similar to herpes febrilis corneae, without formation of vesicles. The onset is characterized by severe acute conjunctivitis, accompanied by pronounced ciliary congestion; there is no secretion or pus, but pronounced lacrimation, pain and photophobia are present. In a few days or weeks the corneal changes follow, in the form of small gray spots, usually numbering ten to twenty, but often reaching one hundred. The foci are scattered over the entire cornea or are massed in the central portion. The individual spots are sharply outlined and consist of minute dots; they are located in the superficial layers of the stroma, the epithelial layer bulging over the infiltrates. When the epithelium is lifted off, the infiltrates in the superficial layers are exposed. The irritation disappears within a short time; on the other hand, the spots persist for many months. The centrally located infiltrates result in visual impairment. In one fourth to one third (more than 30) of Fuchs's cases the condition occurred simultaneously in the two eyes and was equally distributed. The disease

19. Weiss, C.: Bacteriologic Observations on Infection of the Eye, Arch. Ophth. **30**:110 (July) 1943.

20. Adler, H.: Keratitis Subepithelialis, Centralbl. f. prakt. Augenh. **13**:289, 1889.

21. von Reuss, A.: Keratitis Maculosa, Wien. klin. Wchnschr. **2**:665, 1889.

22. Fuchs, E.: (*a*) Keratitis Punctata Superficialis, Wien. klin. Wchnschr. **2**:37, 1889; (*b*) Lehrbuch der Augenheilkunde, Leipzig, F. Deuticke, 1889.

23. von Stellwag, C.: A Peculiar Form of Corneal Inflammation, Wien. klin. Wchnschr. **2**:613, 1889; **3**: 660, 1890.

was often preceded by catarrhal symptoms of the respiratory tract, rarely by herpes of the face. The superficial location of the foci, in conjunction with involvement of the respiratory tract, showed a similarity to herpes. But the absence of a herpetic eruption on the face, the bilateral distribution, the short duration of the acute inflammatory symptoms and, furthermore, the large number of infiltrates constantly present differentiated the condition from herpes. Vesicles, epithelial defects and ulceration did not occur. Involvement of the deeper parts, such as iritis or hypopyon, was not observed. The condition lasted many months, and exacerbations were frequently noted. In 14 of the 18 cases cited in his textbook [22b] the disease persisted for from six months to a year. Only after the lapse of one or two years could one be assured of the complete disappearance of the corneal foci. Prolonged observation of the patients compelled Fuchs to change the opinion stated in his textbook, namely, that ulceration occurs but rarely (in 4 cases). The age of one-half the patients varied from 10 to 20 years, the others being rarely less than 10 years old and frequently 40 or older. Most of the cases occurred in the coldest period of the year, between December and March.

The same epidemic was described by the three other authors. Adler's [20] description of keratitis subepithelialis centralis agreed with that of Fuchs. Von Reuss [21] noted somewhat larger infiltrates, which were peripherally situated in the cornea. Most of the differences existed in von Stellwag's [23] observations, in which the infiltrates appeared coin shaped, measured 1.5 mm. and often showed epithelial defect and ulceration. The infiltrates were not only in the superficial layer of the cornea but in various layers of the stroma; the area of predilection was the periphery, not the center, of the cornea. Iritis was often noted. Healing was rapid, in two to fourteen days, in contrast to the extremely protracted period before clearing up of the lesions reported by the other authors. The differences in the clinical appearance and the duration of the disease led Fuchs to suggest that von Stellwag might have studied a different condition, despite the fact that the disease also was usually bilateral in his cases.

After an interval of eleven years, the disease appeared in Bombay, between January and April of 1901, and disappeared with the approach of hot weather. Herbert [24] observed 226 cases, in which the usual duration was from two to three weeks and the attack was almost invariably limited to one eye. Only in a case of subacute trachoma were both eyes typically involved. In another case in the epidemic the second eye was mildly affected while the first was recovering. There were no symptoms of nasal catarrh. Most of the patients were young adults, those in the 20 to 30 year age group being most commonly affected.

Clinically, the lesion consisted of minute spots, scarcely at all opaque and easily escaping detection until stained with fluorescein. The corneal surface appeared rough, with slight elevation of the epithelium. As the period of healing approached, the eruption tended to be confined to the central part of the cornea. Thickening of the limbus and moderate conjunctival and ciliary congestion formed part of the clinical picture, the latter being of variable degree and often absent.

The disease approached the proportions of a real epidemic in Madras, India, in 1920, 1928 and 1930. The published report was made by Kirkpatrick,[25] who described a greater incidence in males than in females, the disease being most frequent in persons between 25 and 45 years of age (the number was not given). There were absence of local reaction and evidence of general disease or constitutional defect; lacrimation and photophobia were occasionally noted, and the disease was uniocular. Three clinical types were noted. In the first, or superficial, type infiltrates, pinpoint to pinhead in size, irregularly dotted the corneal surface. The disturbance affected chiefly the pupillary area; irritation was noted only when the infiltration was in close approximation to the limbus. A vascular reaction, either circumcorneal or conjunctival, was not noticeable. In the second type the punctate character was lost. One large patch nearly always had a denser portion, which was often linear and somewhat raised. The soft opacity of the large patch faded away into the normal cornea. The patch involved a quadrant of the cornea. This lesion, with possibly a few smaller spots at some distance from it, represented the most common form. The third type was the single, dense, sharply circumscribed spot, with slight elevation and some vascularization when the lesion was situated especially close to the limbus. Irritation was more severe, and the tendency to clear up was less evident in this type than in the first and second types. The duration of the disease varied with the type, the punctate form clearing up in two or three weeks and the last form persisting a year or longer. The epidemic was

24. Herbert, H.: Superficial Punctate Keratitis, Ophth. Rev. **20**:339, 1901.

25. Kirkpatrick, H.: An Epidemic of Macular Keratitis, Brit. J. Ophth. **4**:16, 1920.

not characterized by the frequent accompaniment of corneal herpes.

In his first paper Wright [26] reported 923 cases (1928-1929). The epidemic increased in intensity in the second half of 1929, and by the end of the year he had observed 3,500 cases; by February 1930, the epidemic had practically disappeared. Of the first 923 cases, the disease was unilateral in all but 6 cases, in which it was bilateral. In 2 of these 6 cases the two eyes were attacked at the same time. The duration of the corneal opacities varied from one week to more than a year. In the first series there were 772 males (the incidence being highest between the ages of 20 to 30) and 151 females. In 88 of 225 cases tests with fluorescein gave negative results. Wright emphasized the acute onset, with involvement of the cornea and conjunctiva and the usual occurrence in one eye only. The discrete opacities were localized in the superficial layers of the cornea; they varied in size and number from a multitude of fine gray points, visible only with the loupe, to isolated dots discernible with the naked eye. The epithelium was smooth but might be raised; actual vesiculation was uncommon. The onset was similar to that of mild conjunctivitis and was possibly associated with, or followed by, catarrhal involvement of the respiratory tract. Vision was rarely interfered with to any great extent. There was no iritis, but hypotonia was often present. The relation of superficial punctate keratitis to keratitis disciformis and herpes febrilis corneae produced a different disease picture in each case.

In the first series of cases the external signs were mild; the onset was similar to that of slight catarrhal conjunctivitis or hyperemia, edema of the lid with chemosis suggesting acute inferior conjunctivitis. Photophobia and lacrimation were present. There was almost complete absence of conjunctival discharge. Discomfort was negligible. In the second series the external signs were more pronounced, the eyes having an intensely red appearance, due to increased virulence of the organisms through frequent passage.

The corneal opacities varied from delicate dots, detectable only by the slit lamp, to large solitary, disciform infiltrates. The interval between the appearance of the conjunctival hyperemia and that of the corneal lesions was usually six days, but longer intervals occurred. In some cases the corneal dots showed elevation of the surface and enormous variation in number. In a large majority of cases the infiltrates disappeared in two months; in other cases they persisted as faint, rounded macular spots (occasionally annular), in rare instances resulting in dense white cicatricial tissue. The corneal sensibility proved to be normal, even in the most severe forms of the disease. The commonest lesion consisted of the small gray dots; often at first only one or two dots appeared, close to the engorged and edematous limbus, and in the next day or two the entire cornea might be involved. The enormous variation in the size and number of the lesions, also, was an integral part of this epidemic, the number ranging from one to a hundred. The foci were peripheral or confined to the pupillary area and were quadrantal in form. The lesions appeared in fine curdlike flakes, with ill defined outlines in the epithelium and probable extension into Bowman's membrane. Their elevation frequently produced eminences in the zone of specular reflection. A second type of opacity was angular, sharply defined, densely opaque, usually round and visible with the naked eye. The lesions varied from minute points to large areas measuring 2 mm. in diameter. Large disks developed from smaller ones. Lesions representing transitions from the annular to the disciform type, of 3 mm. diameter, were seen, the latter involving the entire thickness of the cornea, with hazy outlines and pronounced corneal swelling. The lesion of the superficial layers was accompanied, even in the mildest form, by fine deposits of the endothelium and possible folding of Descemet's membrane, with large pigmented deposits, the deposits in rare instances being larger than the superficial opacities.

The bilateral appearance of the disease was more frequent in the second series of cases, occurring in 16 of the last 1,000 cases, as compared with 6 of the first 923 cases. The second series differed, furthermore, in the presence of tenderness of the preauricular glands, which was first noted at the end of the epidemic in 2 cases of a severe form. Once attention was called to the presence of this tenderness, it was found to be part of the clinical picture in 6 cases of less severe form. This feature may have been unnoticed in the earlier cases, but was undoubtedly absent in many cases in which the disease was of average severity.

Viswalingam,[27] in Malaya, observed only 2 cases of the disease in 1934, but between 1925 and 1938 the epidemic produced 3,521 cases (2,366 of males and 1,155 of females). He identified the epidemic with that of macular kera-

26. Wright, R. E.: Superficial Punctate Keratitis, Brit. J. Ophth. **14**:257, 1930.

27. Viswalingam, A.: Epidemic Superficial Keratitis in Malaya, Brit. J. Ophth. **25**:313, 1941.

titis reported by Kirkpatrick, a disease already acknowledged by Wright to be identical with the condition which he described as superficial punctate keratitis and with the disease in the epidemic of 1931-1932 in Bengal, observed by Kirwan.[28] Again, the onset was sudden and unilateral, with possible involvement of the second eye one or two days later. Next to the photophobia and lacrimation, swelling of the lids, especially of the outer third of the upper one, dominated the picture. The swelling gave a baggy appearance in the severe forms, like that in lymphostasis, reminding one of a wasp sting. The palpebral and bulbar conjunctivas between the cornea and the outer canthus were severely inflamed, with subsequent chemosis, which often spread over the entire bulbar conjunctiva. In the great majority of cases hardly any mucoid or purulent discharge was present, but invariably the preauricular gland was swollen, and occasionally the submaxillary gland, and in rare cases even the cervical glands, were enlarged. The infiltrates were punctate and superficial, in some cases uniformly studding the entire cornea and in others being scattered. The spots were grayish and occasionally coalescent; erosion and elevation of the epithelium occurred in rare instances. In some cases the superficial infiltration extended to the deeper layers of the stroma, to Descemet's membrane or even to the uvea. The duration of the lesions was stated to be several weeks, but in some cases the spots persisted for two years. Vesiculation, or blisters, not infrequent in Kirwan's series, were consistently absent. The frequency of involvement of the preauricular gland was more characteristic in this series than in Wright's.

In Tasmania, Hamilton[29] managed an epidemic of 92 cases of keratoconjunctivitis between July 1932 and November 1934; before and after this period only endemic cases were observed. Forty-two males and 50 females were affected; the incidence was highest in males in the third decade of life and in females in the fifth and sixth decades. In 25 of the 92 cases the disease was bilateral; in 6 cases the eyes were simultaneously involved, and in another 9 cases the average interval between the appearance of involvement of the two eyes was seventy-eight days, the minimum period being two days and the maximum eighteen months. In 16 cases a relapse occurred in the affected eye after an interval ranging from three days to four years. In 3 cases the superficial punctate keratitis led to multiple corneal erosions; in 17 cases, to marginal keratitis, with and without ulceration; in 3 cases, to dendritic ulcer, and 1 case, to disciform keratitis. The last complication was observed concurrently with superficial punctate keratitis by other authors, such as Wright and Grueter.

Doggart's[30] study included 43 cases, the disease being unilateral and not associated with any other illness, except in 4 cases. The time required for absorption of the dots was stated to be from a fortnight to many months.

The morphologic concept of superficial punctate keratitis, defined as a definite condition by Fuchs, is applicable to any pathologic lesion consisting of opaque dots which involve the epithelial layer, Bowman's membrane and the superficial layers of the stroma. The reason that this group of lesions forms a definite disease entity is evident when the epidemic proportions, the sudden widespread appearance in different localities after the lapse of many years and the etiologic factors in the epidemic are considered.

The epidemic in Calcutta from July to September 1932 consisted of 175 cases. Sanyal[31] described the disease as usually uniocular and as affecting males more often than females. The onset was characterized by coryza, without elevation of temperature or glandular involvement. Recovery usually occurred within a week or ten days; in 8 per cent of the cases three weeks was required, and in only 1 case did one month elapse before complete disappearance of the symptoms. The corneal lesions were of four forms: (1) the punctate type, most dense in the central portion and fading toward the periphery; (2) the linear type, with the diameter of a hair, consisting usually of one (most common) or two wavy lines, with tapering ends and no branching, the lines crossing each other when double; (3) a combination of the two varieties, and (4) loss of corneal luster, extending from the limbus to the center, or a band of homogeneous opacity completely encircling the periphery of the cornea in somewhat annular fashion. The corneal sensitivity was normal.

During World War I no epidemic of keratoconjunctivitis broke out, but during the present conflagration epidemics of large proportions have

28. Kirwan, E. W.: Epidemic Superficial Punctate Keratitis in Bengal, Folia ophth. orient. **1**:345, 1934.

29. Hamilton, B. J.: Survey of Superficial Punctate Keratitis in Tasmania, with Survey of a Mild Epidemic, Brit. J. Ophth. **25**:1, 1941.

30. Doggart, J. H.: Superficial Punctate Keratitis, Brit. J. Ophth. **17**:65, 1933.

31. Sanyal, S.: Epidemic Superficial Keratitis, Am. J. Ophth. **16**:390, 1933.

been observed in Germany and in the United States.

From March to October 1938, zur Nedden [32] observed 127 cases of superficial punctate keratitis. The condition was characterized by an incubation period of eight days and a long duration, extending as a rule to three months. In a second report on observations through a continued period, up to February 1939, the number of cases was stated to rise to 200, and in a third paper the number was reported to be 500. In the majority of cases the occurrence was spontaneous, but in 35 per cent superficial injuries preceded the disease. Chemosis of the conjunctiva, swelling of the lids and the preauricular gland, follicular conjunctivitis and subconjunctival hemorrhages were associated with punctate superficial lesions of the cornea. Involvement of the conjunctiva was usually bilateral; the cornea was rarely involved. Males between 20 and 50 years of age were chiefly affected; children below 12 were free from the disease. Sensibility of the cornea was normal; the epithelial cover of the lesions was loose and easily removable with forceps. The punctate changes were of long standing, the dots being visible even after nine months, and the coin-shaped lesions outlasted even the punctate foci. In 1 case there was a duration of two years. In 5 cases keratitis filiformis was noted. According to zur Nedden, no relation exists between superficial punctate keratitis and herpes.

Smitmans [33] reported about 150 cases of epidemic keratoconjunctivitis, in which the onset began with catarrhal symptoms of the nose and throat, or in rare instances with griplike symptoms, accompanied by fever. The disease was characterized by swelling and inflammation of the conjunctiva; chemosis; petechial hemorrhages; seromucous, nonpurulent secretion, and swelling of the lymph glands. The corneal infiltration was intraepithelial in the central portion but extended into the superficial layers of the stroma at the periphery. In the early stages the infiltrates stained with fluorescein. The corneas of both eyes were usually involved, in some cases to a very slight degree, as revealed by examination with a slit lamp. Vascularization and iritis were not observed. The period of incubation was five to ten days.

Ohm [34] observed 700 cases without conjunctival hemorrhages, the absence of which is also characteristic of conjunctivitis due to pneumococci. Swelling of the preauricular glands, with a slight rise in temperature, was often noted. Involvement, even in the severe forms, was frequently unilateral. In about 50 per cent of cases corneal complications were present in varying degreees of severity after the clearing up of the conjunctival changes. The infiltrates, measuring 2 to 3 mm., were usually centrally located and extended below Bowman's membrane; they showed improvement only at the end of six to eight weeks. Dendritic keratitis did not appear in this series of cases, but herpetic vesicles, covering the entire cornea, were of common occurrence, especially toward the end of the epidemic.

Senger [35] first reported about 500 cases, and later another series of about 500 cases. Corneal complications occurred in 30 to 40 per cent of the cases, as a secondary infection, the epithelial layer being involved. The disease was usually unilateral, with chemosis of the conjunctiva, edema of the lids, subconjunctival and subcutaneous hemorrhages and swelling of the preauricular gland. Like Senger, Goedbloed [36] described the clinical manifestations of the epidemic as characteristic of superficial punctate keratitis, with catarrhal rhinitis but without swelling of the preauricular gland. Possibly the nose is the portal of entry, but primary infection of the eye is not excluded in some cases. Schwitalla [37] reported 129 cases with typical onset, unilateral involvement, conjunctival hemorrhages, swelling of the preauricular gland and diminished sensitivity of the cornea. Ulceration was not observed. Males were chiefly affected. Of 129 cases, the condition was unilateral in 106 cases and bilateral in 23 cases.

In the German epidemic different designations were used—keratitis superficialis epidemica (Schultze [38]), keratoconjunctivitis epidemica (Schneider [39]), keratoconjunctivitis of 1938

32. zur Nedden, M.: Epidemic of Keratitis Superficialis, Klin. Monatsbl. f. Augenh. **101**:567, 1939; Keratitis Superficialis, ibid. **102**:487, 1939; Observations on Five Hundred Cases of Epidemic Keratoconjunctivitis, ibid. **105**:424, 1940.

33. Smitmans, F. K.: Symposium on Epidemic Keratoconjunctivitis, Med. Klin. **35**:235, 1939.

34. Ohm, W., in discussion on Smitmans.[33]

35. Senger, W.: Conjunctival Disease of Unknown Origin, München. med. Wchnschr. **85**:1810, 1938; **86**: 607, 1939.

36. Goedbloed, J.: Keratoconjunctivitis Punctata Superficialis, Ophthalmologica **99**:436, 1940.

37. Schwitalla, H.: Epidemic of Keratoconjunctivitis Nummularis (Dimmer), Klin. Monatsbl. f. Augenh. **102**:491, 1939.

38. Schultze: Keratitis Superficialis Epidemica, Klin. Monatsbl. f. Augenh. **102**:425, 1939.

39. Schneider, R.: Epidemic of Keratoconjunctivitis in Munich and Surroundings, München. med. Wchnschr. **85**:1981, 1938.

(Smitmans [33]), superficial punctate keratitis (zur Nedden [32]; and Bartels and Loens [40]), epidemic herpetic keratitis (Becker [41]) and keratoconjunctivitis nummularis Dimmer [42] (Meissner,[43] Ješe,[44] Schwitalla [37]). Most of the observers in the English literature and part of the German authors, although using different designations, accepted Fuchs's classification of superficial punctate keratitis. The group following Dimmer, however, classified the disease clinically as nummular keratitis.

Dimmer [42] reported 4 cases of corneal disturbance; he described the lesions as corresponding closely to those originally described by von Stellwag but as differing notably in having a duration of many months, in contrast to the rapid healing within ten to twelve days in von Stellwag's cases. Salzmann [45] collected 88 cases of the disease, the lesions being unilateral in 86 cases and present simultaneously in the two eyes in 1 case. In 1 case an interval of four years preceded the involvement of the second eye. In Salzmann's opinion, superficial punctate keratitis and nummular keratitis differ only quantitatively, multiplicity of foci and formation of facets being characteristic of both. In superficial punctate keratitis there is slight conjunctivitis, without secretion but with pronounced ciliary congestion. From the start the disease represents a keratitis, the congestion of the conjunctiva being only symptomatic. In the nummular variety of keratitis the individual foci are large, with a diameter of 2 or 3 mm., but even larger ones are not exceptional, especially lesions with irregular outlines. In the later stage the surface is depressed, but the failure to stain with fluorescein indicates that the epithelial covering is intact. The formation of facets is explained by the location of the infiltrate below Bowman's membrane, so that a slight depression of the membrane occurs in the stage of resorption. The presence of facets on the corneal surface belongs not only to the picture of nummular keratitis but to that of superficial punctate keratitis, contrary to the observation of other authors (Aust [46]).

Aust [46] based his opinion on 27 cases of keratitis nummularis, occurring within seven years, the period coinciding with that of Salzmann's [45] observations. The majority of the patients (20 of 27) were farmers. Almost without exception, the involvement was unilateral (Dimmer and Aust each noted 1 case of bilateral involvement) and was not associated with irritation of the eyes; the conjunctiva was almost normal; even when the disease was bilateral, the two eyes were not attacked simultaneously. The foci usually numbered ten, and often twenty, in 1 case twenty-two foci, usually occupying the central portion of the eye, were noted. Depending on the stage of development, the dots were of three types, with numerous transitional forms: (1) the superficial small dots, 0.5 mm. in diameter; (2) the coin-shaped dots, from 1 to 1.5 mm. in diameter, and of long standing, which were somewhat deeper and were associated with swelling of the cornea, folding of Descemet's membrane, slight cloudiness of the aqueous and almost imperceptible irritation of the iris, and (3) formation of facets. Depression of the corneal surface was present even years later, the formation of facets being as characteristic as the multiplicity of the foci. Sections revealed a normal Bowman membrane, with thinned-out stroma. Aust noted the presence of facets one year, and Salzmann even ten years, after the acute stage of the disease. Vascularization occurred in 2 of Dimmer's [42] 4 cases. There was no recurrence, but healing was extremely protracted; four to five months might elapse before the formation of facets began. Aust disagreed with Salzmann in that he denied that the nummular type was identical with the superficial punctate type of keratitis. Only the multiplicity of dots is common to the two diseases. The superficial punctate variety may exhibit as many as a hundred dots, which necessarily are extremely small, even smaller than the usual dots, of 0.5 mm. diameter. Furthermore, the dots disappear completely, without formation of facets. The nummular variety rather resembles disciform keratitis, the disk-shaped configuration, the absence of ulceration, the location in the upper layers of the stroma and,

40. Bartels, M., and Loens, M.: Causative Agent of Epidemic Keratoconjunctivitis, Klin. Monatsbl. f. Augenh. **106**:83, 1941.

41. Becker: Epidemic Herpetic Inflammation of the Eyes, Klin. Monatsbl. f. Augenh. **102**:866, 1939.

42. Dimmer, F.: Nummular Keratitis and Related Inflammation of the Cornea, Ztschr. f. Augenh. **13**:621, 1905.

43. Meissner, W.: Epidemic of Nummular Keratitis (Dimmer) in Bavaria, München. med. Wchnschr. **85**: 1939, 1938; Nature of Epidemic Occurring in Germany in 1938-1939, Deutsche med. Wchnschr. **66**:517, 1940.

44. Ješe, L.: Nummular Keratitis, Klin. Monatsbl. f. Augenh. **96**:219, 1936; **100**:874, 1938; Keratitis Nummularis Epidemica, ibid. **103**:97, 1939.

45. Salzmann, M.: Keratitis Associated with Herpes, Verhandl. d. ophth. Gesellsch. **42**:303, 1928; Keratitis Nummularis (Dimmer), Arch. f. Ophth. **132**:399, 1934.

46. Aust, O.: Keratitis Nummularis, Dimmer, Arch. f. Ophth. **129**:576, 1933; Epidemic Nummular Keratitis, Ztschr. f. Augenh. **82**:167, 1933.

finally, the long duration, without any irritative symptoms, being characteristic of both types. The disciform variety, with its large long centrally located patch, differs from the nummular form, with its multiple and smaller foci. Furthermore, the concentric arrangement is usually missing in nummular keratitis. The disciform variety never shows facets but is known to recur; on the other hand, the nummular type does not show recidivation. In spite of some resemblance to keratitis disciformis, the nummular form represents a distinct condition. With regard to the etiologic aspect, Aust, again, differed from Salzmann, the latter stating that the disease was of possible herpetic origin, while the former assigned it a mycotic origin. The occurrence of the disorder in the summer months (from August to September) probably gives additional support to the mycotic theory. In the subsequent discussion on Aust's paper, Lindner expressed the opinion that the disease is possibly mycotic, and A. Fuchs compared it to "rice mud" keratitis, seen in the Netherland East Indies and in Ceylon. On the other hand, on the basis of his experience in 25 observed cases, in 1 of which the disease was bilateral, Szekely [47] fully accepted Salzmann's opinion. He stated that keratitis nummularis, keratitis vesiculosa and keratitis punctata superficialis are members of the same disease group and are closely associated with keratitis disciformis; in 1 case of keratitis vesiculosa development into keratitis disciformis could be observed. Neame's [48] opinion gave further support to this concept, namely, that superficial punctate keratitis and its grosser forms—nummular and macular keratitis and dendritic ulcers—are different forms of infection with the herpes simplex virus. His observations in a case of dendritic ulcer with two spots of macular or nummular keratitis together with herpes of the mouth and lids, and in another case of superficial punctate keratitis and two small dendritic ulcers with facial herpes speak not for a coincident but for an identical origin.

Meissner's [43] observations during the epidemic of keratoconjunctivitis in Germany led him to the conclusion that the disease belonged to the keratitis nummularis type (Dimmer). The conjunctival changes were atypical, and the diagnosis was certain only when the cornea became involved. Ulcerations did not occur, but recurrence was not uncommon. The corneal sensitivity diminished, as in herpes. Jancke [49] agreed with Meissner as to the clinical classification. Ješe [44] reported 77 cases in his first article and 47 in his second article. In 43 of the first 77 cases, the condition occurred in farmers; usually the disease appeared in September. In all but 4 cases the disease was unilateral. The multiplicity of foci was conspicuous, the average number of infiltrates being ten. There were five or less lesions in 16 cases, eleven to fifteen lesions in 10 cases, sixteen to twenty lesions in 4 cases; twenty-one to twenty-five lesions in 5 cases, twenty-six to thirty lesions in 2 cases and thirty-two lesions in 1 case. Clinically, the lesions presented the picture outlined by Salzmann [45] and Aust [46]; round infiltrates of densely packed dots, which were gray and later yellowish, and were of unequal size and arranged in groups, of superficial location. The foci had a long duration and terminated in formation of facets. Contrary to the opinion expressed by Aust, vascularization was frequent. The same feature was mentioned by Dimmer [42] and was noted frequently by Salzmann, especially in cases in which the infiltrates were close to the limbus. Deposits developed in 4 of the cases and iritis in 1 case, and confluent patches often caused folding of Descemet's membrane. Ješe [44] theorized on the possibility that the disorder belonged to the herpes group, as postulated by Salzmann, who observed the transition of the nummular into the dendritic type and of the dendritic into the disciform type. His concept was further supported by his observation of the simultaneous presence of herpes simplex corneae in 2 instances. In 1 of these, a case of recurring herpes, the transition to keratitis nummularis was demonstrated. Contrary to the opinion expressed by Aust, Salzmann's assumption that the onset consists in the appearance of multiple lesions within the cornea has been corroborated. Reichling's observation of keratoconjunctivitis epidemica in one eye and dendritic keratitis in the other is further evidence in support of a herpetic origin. Becker [41] compared the disease in his cases to the keratitis epithelialis vesiculosa disseminata described by Vogt, which was characterized by two to ten epithelial vesicles or defects, often accompanied by herpes of the lips. In Sácha's [50] 2 cases,

47. Szekely, J.: Keratitis Nummularis (Dimmer), Arch. f. Ophth. **134**:184, 1935.

48. Neame, H.: The Association of Dendritic Ulcer of the Cornea and of Superficial Punctate Keratitis with Herpes Facialis, Brit. J. Ophth. **21**:298, 1937.

49. Jancke, G.: Mechanism of Development of Nummular Keratoconjunctivitis Epidemica, Klin. Monatsbl. f. Augenh. **105**:7, 1940; Identity of Keratoconjunctivitis Nummularis Epidemica and Diseases Described from 1889 to 1941 Under Various Names (Keratitis Punctata, Nummularis, Maculosa, Epidemica, etc.), ibid. **108**:39, 1942.

50. Sácha, A.: Keratitis Nummularis (Dimmer), Arch. f. Ophth. **131**:102, 1933.

those of a 5 year old girl and a man aged 22, the disease was of the same type, the diagnosis being based on quantitative, rather than on qualitative, differences, the second case having features similar to those of disciform keratitis.

Scheerer [51] emphasized the stubborn resistance to treatment and the frequent recurrence. His cases were characterized by mild conjunctival symptoms, with corneal complications occasionally at the onset, the corneal lesions staining with fluorescein. The changes in the cornea were protean and involved the epithelial, subepithelial and superficial layers as dustlike, delicate pointlike or larger spots. They were scattered as irregular projections over the entire cornea, with a predilection for the center. Sometimes delicate folding of Descemet's membrane and slight hyperemia of the iris were observed, as well as plastic iritis, in 1 case. Opacities in the vitreous and episcleritis, frequently with a swollen preauricular gland, were also noted. The early stages were similar to those of superficial punctate keratitis; the late stages resembled the nummular type.

Meesmann and Bachmann [52] reported 250 cases in which there were swelling and redness of the caruncula, and later the semilunar fold, and often ptosis. Follicles were present on the inflamed upper fornix; swelling of the preauricular gland was noted in severe forms of the disease. The severity of the corneal complications was inversely related to that of the conjunctival symptoms. The severe form of conjunctivitis healed within three or four weeks without any corneal involvement. In 15 per cent of cases the cornea was involved, with a duration of four to five months. Healing did not produce immunity; in a case of unilateral, severe conjunctivitis, lasting three months, the second eye became affected after an interval. The sensitivity of the cornea was diminished. The corneal lesions appeared first in the center and later in the periphery. They extended from the superficial into the deeper layers, and healing left a mild depression of the surface, as a result of absorption, with subsequent irregular astigmatism. Wolter [53] expressed the belief that epidemic keratoconjunctivitis was nummular in form, iritis and cloudiness of the aqueous, with swelling of the lymph glands, being present only in exceptional cases.

The first observation of American authors on the epidemic was made by Merrill,[54] who described clinical manifestations similar to those outlined by Wright. Several members of the same family had the disease, the duration of which was from three to eighteen months, in some cases even longer. Swelling of the preauricular gland was observed only in rare instances. Hobson [55] reported about 16 cases, in which the onset was marked by violent conjunctivitis (unilateral only in 1 case). The bulbar and the palpebral conjunctiva were equally red and swollen in the two eyes. In contrast to the similar involvement of the conjunctivas of the two eyes, the cornea of one eye was more severely affected than that of the other eye. The number of stainable dots varied from twenty to one hundred; they were minute and grayish and were situated in the second layer of the cornea. One patient had a corneal ulcer, with the triangular base down. The peculiar arrangement of the deposits may be explained by their mode of origin. Hobson stated:

> They are conglomerations of cells held in masses by . . . fibrin. Motion of the eyeball and gravity may have played a part in placing them in this position. With the aid of a slitlamp it was possible to make out very minute deposits forming a faint haze on the basal layers of the corneal epithelium. In our more severe cases, the cornea appeared rough and uneven.

Thygeson [56] observed that follicular hypertrophy of the conjunctiva was more pronounced in the lower fornix, in association with an enlarged preauricular gland and scanty secretion, composed of mononuclear elements. Complete resolution required from one to three weeks. Bacteriologic examination gave negative results. The lesions appearing in a minor epidemic in Iowa in 1935 resembled the follicular type of inclusion conjunctivitis but differed in the predominance of mononuclear elements (in contrast to the presence of neutrophilic leukocytes in the acute stage of inclusion conjunctivitis), in a shorter duration and in the absence of inclusion bodies. In similar cases observed in New York the lesions were bilateral, with 1 exception. In the latter cases the disease showed acute papillary conjunctivitis, with absence of bacteria and with preauricular adenopathy and scanty secretion, consisting predominantly of mononuclear elements, a picture which led Thyge-

51. Scheerer, R.: Epidemic Keratoconjunctivitis, Klin. Monatsbl. f. Augenh. **105**:110, 1940.

52. Meesmann, A., and Bachmann, W.: Clinical and Microbiologic Observations in Cases of Epidemic Keratoconjunctivitis, Klin. Monatsbl. f. Augenh. **105**:1, 1940.

53. Wolter, H.: Epidemic Ophthalmia (Keratoconjunctivitis Nummularis Epidemica) in Germany, Klin. Monatsbl. f. Augenh. **107**:113, 1941.

54. Merrill, H. G.: Epidemic Keratoconjunctivitis Diversiformis, Am. J. Ophth. **19**:1007, 1936.

55. Hobson, L. C.: Acute Epidemic of Keratitis Punctata Superficialis, Am. J. Ophth. **21**:1153, 1938.

56. Thygeson, P.: A Papillary Type of Béal's Conjunctivitis, Am. J. Ophth. **21**:1017, 1938.

son to the conclusion that the disease was a papillary form of Béal's conjunctivitis.[57]

Hogan and Crawford [58] made an extensive and scholarly study of keratoconjunctivitis epidemica, based on 125 cases. In 31 instances conjunctivitis developed in the second eye after three or four days. When the eyes were involved simultaneously, the condition was more severe, with petechial, or even larger, conjunctival hemorrhages. The average duration of the conjunctivitis was stated to be thirteen days. Keratitis developed in 92 cases and was bilateral in 23 cases. Involvement of the cornea appeared two to eight days after the onset of the conjunctivitis. The intense pathologic condition of the conjunctiva was not associated with a discharge. In 7 of Hogan and Crawford's cases a white, fairly thick, extensive pseudomembrane developed, an observation not reported in previous epidemics. The conjunctivitis was of the follicular type in 54 instances. Preauricular, angular, submaxillary or cervical adenopathy was often noted. The sensitivity of the cornea was normal. The corneal changes themselves were classified under three types: (1) the punctate type, in which the lesions stained with fluorescein, were evanescent and healed with regression of the conjunctival involvement; (2) the macular type, characterized by absence of staining, predilection for the center of the cornea, absence of either ulceration or vascularization, folding of Descemet's membrane, in 6 cases, and a tendency to become faint within three months, and (3) the disciform type, with infiltration of 4 mm. in diameter. The last form persisted longest and resulted in the poorest visual recovery.

Rieke [59] treated 600 patients with the disease in Portland, Ore., in 1941, the condition being unilateral in most cases. In some instances the second eye became involved, but the symptoms were not as severe as those of the primarily affected eye. Small hemorrhages were of common occurrence. Desquamation of the conjunctiva occurred in ten or twelve days. The duration of the disease averaged from twelve to twenty-eight days, being not less than twelve days in any case. In about 50 per cent of the cases grossly visible dots, 0.5 mm. in diameter, appeared on the cornea in large numbers in twelve to fourteen days. Ulceration and vascularization were absent. At the end of two months there was no change in the pathologic picture of the cornea. Only after seven months was diminution in the size and number of the dots observed.

Berliner [60] reported about 18 cases, in 9 of which the condition was bilateral and in 14 accompanied by corneal opacities. The opacity became less intense only after three months. Sanders and Alexander,[61] Sanders and associates [62] and Sanders, in an address at a meeting of the New York Academy of Medicine, section of ophthalmology, stated the opinion that the condition was a disease entity. The diagnosis was made according to the following criteria, based on observations in 80 cases: [62] The presence of an acute follicular type of conjunctivitis, with occasional pseudomembrane of the conjunctiva of the lower lid, and absence of bacteria. In addition, enlargement of the lymph nodes, scanty discharge, composed of mononuclear cells, and superficial punctate keratitis were almost constant features. In 42 cases the cornea became involved from one week to ten days after the onset of the disease, with no record of absorption at the end of five months. All the patients with severe ocular involvement had systemic symptoms, and in 70 of 80 patients the epidemic keratoconjunctivitis followed ocular trauma or inflammation. In the discussion at the meeting of the Academy, Braley [63] referred to 200 cases of his own, in which the diagnosis was based on 1,600 cases recorded in a survey of the New York state department of health.

Sporadic cases of the disease have appeared all over the world, the first outbreak of epidemic proportions occurring in Vienna in 1889. In the Far East the disease is endemic; there the largest epidemics seem to have occurred in peacetime. As previously mentioned, in the last decade the epidemic became rampant in Germany (Düsseldorf; Munich) and in the United States (on the west and east coasts), where it was more prevalent in cold weather, dying out toward spring.

Observers have expressed almost unanimous agreement concerning the absence of bacteria in the epidemic outbreaks, with the exception of Herbert.[24] He described bacilli with a distinct

57. Béal, R.: A Specific Type of Acute Follicular Conjunctivitis, Ann. d'ocul. **137**:1, 1907.

58. Hogan, M. J., and Crawford, J. W.: Epidemic Keratoconjunctivitis, Am. J. Ophth. **25**:1059, 1942.

59. Rieke, F. E.: Epidemic Conjunctivitis of Presumed Virus Causation, J. A. M. A. **119**:942 (July 18) 1942.

60. Berliner, M. L.: Epidemic Keratoconjunctivitis, Am. J. Ophth. **26**:51, 1943.

61. Sanders, M., and Alexander, R. C.: Epidemic Keratoconjunctivitis: I. Isolation and Identification of a Filtrable Virus, J. Exper. Med. **77**:71, 1943.

62. Sanders, M.; Gulliver, F.; Forchheimer, L. L., and Alexander, R. C.: Epidemic Keratoconjunctivitis, J. A. M. A. **121**:250 (Jan. 23) 1943.

63. Braley, A. E., in discussion on Superficial Punctate Keratitis, Keratoconjunctivitis, Arch. Ophth. **30**:160 (July) 1943.

capsule and feeble staining qualities; the organism was twice as long as broad and tapered at the ends, which were round, or sometimes slightly curved. Generally the bacilli were single; only rarely were they paired. Experiments in cultivation and inoculation from eye to eye yielded negative results. Axenfeld and Westhoff concurred in Herbert's opinion, but in subsequent epidemics the organism could not be identified. The large number of specimens collected during the epidemic in Bombay were examined by Wright [26] for the presence of bacteria, with negative results. In the widespread epidemics reported by Viswalingam [27] and zur Nedden [32] the results of bacteriologic studies were negative. Smitmans [33] mentioned the presence of mixed bacteria, such as are noted in all cases of acute conjunctivitis, but inoculation of the cornea of the rabbit, as well as intraocular and intracerebral inoculation, gave negative results. Zur Nedden noted diplobacilli and inclusion bodies in the corneal epithelium in 3 of 10 cases in which he made examination, but he refused to attribute any etiologic significance to these observations, especially since some authorities still doubt that these bodies represent living organisms. The inclusion bodies were absent in the cases of his later series. Inoculation of the rabbit cornea did not produce any significant pathologic changes. Meesmann and Bachmann [52] noted a diphtheroid (Bacillus xerosis) in symbiosis with staphylococci; Behr [64] and Behr and Zeissler,[65] similarly, discovered diphtheroids in their cases. Meesmann and Bachmann concluded that the etiologic role of the micro-organisms of the diphtheroid group was not established, while the latter accepted the diphtheroid as the causal agent, the action of the organisms being weakened as a result of change in virulence. As a logical consequence, diphtheria antitoxin was employed, with good results. Zur Nedden had already taken an energetic stand against Behr and Zeissler's view and ascribed the apparently good results of diphtheria antitoxin to its being a nonspecific therapeutic serum. He noted that children are not subject to epidemic keratoconjunctivitis and, conversely, that they are more susceptible to diphtheria than are adults. Furthermore, from the bacteriologic standpoint, it is worth mentioning that bacilli of the xerosis group are less toxic but may acquire some degree of toxicity in cases of acute conjunctivitis. The possible pitfall in the use of diphtheria antitoxin in treatment of keratoconjunctivitis was pointed out also by Wolter,[53] who called attention to the fact that often the disease disappears spontaneously without any medication or, as in Meissner's case, through the administration of saline solution exclusively. In the epidemic of 1928 Bartels and Loens [40] found B. xerosis in the corneal epithelium of patients with superficial punctate keratitis.

The absence of characteristic and constant bacteriologic features did not escape the attention of observers and, consequently, led to another possible explanation of the epidemics, namely, their virus origin. In the earlier years this explanation was necessarily speculative, while in later years, since Grueter's epochal transmission of dendritic keratitis to the cornea of the rabbit, the theoretic suppositions have been replaced by experimental research. These scientific efforts were crowned recently by the success of Sanders and his co-workers in isolating the virus.

The possible herpetic origin, through an attenuated, altered or different virus, had already been suggested by Fuchs, who pointed out that with respect to the location of the infiltrates in the superficial corneal layers and the association with involvement of the respiratory tract, epidemic keratoconjunctivitis resembles herpes but differs from it in the absence of a herpetic eruption on the face, in the absence of vesicles, in the multiplicity of foci, in the more frequent bilateral occurrence and, finally, in a shorter duration. The discovery of the transmissibility of corneal herpes was made by Grueter, in 1918, and after this the occurrence of the major epidemics of keratoconjunctivitis necessarily influenced the search for their causation. Grueter differentiated two forms of herpes virus, the more virulent one being responsible for dendritic keratitis and the less virulent one for the superficial punctate, vesicular and disciform varieties of the disease and for the recurrent corneal erosion. According to Salzmann,[45] the herpes virus is capable of producing various types of lesions, and the superficial punctate type of keratitis is intermediate between the vesicular and the disciform type. Ješe [44] accepted the explanation without any investigation of his own. Zur Nedden [32] denied the existence of any relation between superficial keratitis and herpes and obtained negative results from inoculation of the rabbit cornea. Meissner [43] had similar negative results with the same technic, but both authors, together with Schwitalla,[37] Smitmans [33] and Jancke,[49] accepted the theory of a virus causation. Jancke emphasized that the virus of keratoconjunctivitis cannot be identical with the herpes virus because

64. Behr, C.: Keratoconjunctivitis Epidemica, Deutsche med. Wchnschr. **66**:515, 1940.

65. Behr, C., and Zeissler, J.: Etiology of Epidemic Keratoconjunctivitis, München. med. Wchnschr. **87**: 665, 1940.

the former does not show an increase in virulence after animal passage and does not result in general symptoms, not even after intracerebral inoculation. Inoculation of the cornea of rabbits and guinea pigs yielded positive results only in a small percentage of cases, and the disease occurred in milder form than in man. Of 42 corneal inoculations, 14 gave positive results, the lesion consisting of infiltration in the area of the scratch and slight conjunctivitis, with swelling of the lids; dendritic keratitis occurred in only 1 instance. The insertion of pieces of infected human conjunctiva into the conjunctiva of rabbits resulted in the occurrence of various lesions, such as follicular conjunctivitis and punctate and disciform keratitis. Material scratched on the corneas of 15 rabbits produced tonguelike infiltrations radiating from the scratch in 10 animals. Therefore the virus must be related to the herpes virus, or to a similar filtrable virus. The diminished sensitivity of the cornea and the herpetic complications in some cases of punctate keratitis point either to this possibility or to the production of a favorable disposition to herpetic invasion. The petechial hemorrhages of the skin were interpreted by Hamilton [29] as neural lesions due to the virus, and he cited Neame,[48] in whose opinion it was almost certain that one virus, modified perhaps in different localities or in different years, is capable of producing a variety of corneal lesions. Hamilton noted absence of acquired immunity. This is not surprising, since it is known that antibodies are numerous after infection with herpes simplex but do not provide lasting immunity.

With regard to the question of virus causation, Wright observed nuclear and cytoplasmic inclusion bodies suggestive of Negri bodies rather than of the inclusions characteristic of variola. The inclusion bodies were numerous, of varying size and staining quality and in close proximity to the corneal lesion. In 5 of 7 specimens the corneal epithelium stained with hematoxylin and eosin, and patches of minute, ovoid or elongated particles lay on the cells; these particles were not seen in scrapings, could not be cultivated and were thought to be rod organisms. The transfer of an unfiltered suspension of epithelium to the cornea of rabbits produced the disease on the sixth day in 1 of 2 black rabbits and failed to produce the condition in 7 white rabbits. Direct transfer to the cornea gave positive results in 3 of 7 human subjects and negative results in 13 monkeys. Attempts to transfer the disease to the skin of human subjects, as well as to the skin of rabbits and calves, and subdural and intratesticular injections in rabbits resulted in failure. Filtered material planted on the cornea gave positive results in 5 of 11 human subjects and negative results in white and black rabbits and in monkeys. In conclusion, Wright decided that the agent in the disease must be a specific filtrable virus. Encouraged by these experimental results, Viswalingam [27] instilled conjunctival washings into healthy eyes and produced the disease in 4 of 6 persons, with corneal involvement in 1 of them. The conjunctivitis developed within twelve to thirty-six hours; it was moderately severe and was associated with chemosis and swelling of the preauricular gland. Dresel reported 4 successful "takes" in 8 inoculations of the chorioallantois of chicks, the 9 or 10 day embryos dying in from seventy-two to ninety-six hours after the appearance of edema and opacification of the membrane. In 1 experiment the virus passed through 4 embryos without losing its specificity. Meissner [43] and Goedbloed [36] had negative results in inoculation of the rabbit cornea, and Smitmans [33] had negative results in intracorneal and intracerebral, as well as in corneal, inoculations. Their failure to produce the disease was interpreted as ruling out the possibility that herpes virus was the causative agent, since the rabbit cornea is sensitive to this virus. All these authors and, in addition, Bartels and Loens [40] worked on the assumption that a virus was the causative agent.

The most important experimental work was that of Sanders and Alexander,[61] who succeeded in isolating the virus from the blood of 2 patients. At first, the virus could be sustained by inoculation of tissue cultures with conjunctival scrapings or with emulsified mouse brain. Later, injections of the virus proved fatal to every mouse to which they were given, and the virus could be readily maintained in mice. The virus proved pathogenic for unweaned white Swiss mice when injected intravenously, intraperitoneally and intracerebrally, and for rabbits only when given intracerebrally. The virus passed through E-K Seitz and Berkefeld filters. The mouse virus was not neutralized by anti-lymphocytic-choriomeningitis serum, antiherpes serum or normal human serum. But neutralization of the virus occurred with serum of the 2 patients from whom the virus was isolated and, furthermore, with the convalescent serum of 3 patients from California and 1 patient from New York who had previously had epidemic keratoconjunctivitis. The mouse virus proved to be slightly pathogenic in a human volunteer, whose serum contained neutralizing antibodies after one month. Antibodies were demonstrated in 7 patients.

The isolation of the virus in cases of epidemic keratoconjunctivitis firmly established the disease as a clinical entity, in the same way in which the transmission of dendritic keratitis distinguished the latter from other corneal diseases. The question whether superficial punctate keratitis and nummular keratitis are two varieties of the same disease or are distinct diseases will find a definite answer only in further research. At present opinions differ. Fuchs expressed the belief that the disease picture described by von Stellwag differed so widely with respect to its short duration and the complete recovery of the patient that it might represent a different clinical entity. Dimmer revived the conception of nummular keratitis; Salzmann, Szekely and others stated they would include disciform keratitis in the herpetic group. The isolated occurrence of facial herpes and dendritic or vesicular keratitis with, or preceding, epidemic keratoconjunctivitis seems to support this contention, without furnishing decided evidence. The clinical similarities and dissimilarities previously mentioned neither prove nor disprove the assertion. It is of interest that in the epidemic in Germany some authors seemingly observed clinical manifestations characteristic of superficial punctate keratitis, and others described the disease as nummular keratitis. It has been stated by some observers that when not epidemic the latter form was of mycotic, not virus, origin (Aust; Lindner), that it occurred in farmers and that it terminated in formation of facets. Observations by Ješe, Meissner, Schwitalla, Pillat and Jancke favored the belief that the disease is the nummular type of epidemic keratoconjunctivitis, notwithstanding the fact that in the same epidemic superficial punctate keratitis was the predominant form in the observations of zur Nedden and others, as well as in the epidemics of the Far East and of the United States. There are two possible explanations: Either the same virus causes clinically similar, but not identical, lesions, or the epidemic is caused by two different viruses or by a virus and an attentuated form. But the virus of epidemic keratoconjunctivitis differs widely from that of corneal herpes, as proved by Sanders; consequently, there exists a clinical and biologic differentiation, which must be taken into account. The possibility that epidemic keratoconjunctivitis is identical with Béal's conjunctivitis can be eliminated in view of the absence of neutralizing antibodies in cases of Béal's disease, as well as the absence of corneal complications, which is one of the most important features in epidemic keratoconjunctivitis.

TRACHOMA

Halberstaedter and von Prowazek,[66] in 1907, reported cases in Batavia, Netherland East Indies, in which cellular inclusions occurred in the epithelial cells of the conjunctiva and the disease was transmitted, with identical inclusions, to orang-utans. The minute bodies were first recognized by von Prowazek as the causative agent in trachoma. This cellular inclusion proved to be morphologically identical with that in psittacosis, which, through experiments with collodion membrane filters, was discovered much later to be a filtrable virus of comparatively large size. After this discovery an enormous amount of literature appeared showing that the inclusions are most numerous in the superficial epithelium in cases of untreated acute trachoma, are less frequent as the disease progresses and are present in only 50 per cent of cases of long-standing disease. The Giemsa or the Heidenhain iron hematoxylin stain is useful in demonstrating their presence. With the Giemsa stain the inclusions appear light blue, violet or red, and the tiny extracellular granules are uniformly red. Von Prowazek[67] designated the cellular inclusion as a chlamydozoon, to indicate the protistan nature. Confirmatory observations were shortly reported by Stargardt, von Kenedener, Miyajima, Mijaschita, Leber and Greeff, who gave the name trachoma bodies. This term was subsequently changed to elementary bodies, or organisms, by Herzog.[68]

These organisms are now recognized as identical with elementary bodies in other virus diseases. The particles, 0.25 millimicron in diameter, are surrounded by a halo of nonstaining material, frequently exist in pairs and sometimes are connected by a slender filament. The large inclusion bodies are located in the cytoplasm and occasionally in the nucleus. Clumps of elementary bodies are constantly observed in the cell cytoplasm, a small or a large compact mass lying free in the plasma or capping the nucleus. The minute bodies may be so numerous that the entire cytoplasm appears studded with them, or they may be evenly distributed, each being embedded in a pale blue–staining mass of the

66. Halberstaedter, L., and von Prowazek, S.: Cellular Inclusions of Parasitic Nature in Trachoma, Arb. a. d. k. Gsndhtsamt. **26**:44, 1907; Deutsche med. Wchnschr. **2**:1285, 1907; Significance of Chlamydozoa in Trachoma and Blennorrhea, Berl. klin. Wchnschr. **46**: 1110, 1909; **47**:661, 1910.

67. von Prowazek, S.: Chlamydozoa, Arch. f. Protistenk. **10**:336, 1907.

68. Herzog, H.: A New Method of Rapid and Contrast Staining of Trachoma Bodies in Histologic Sections, Arch. f. Ophth. **74**:520, 1910.

protoplasm, which Halberstaedter and von Prowazek called plastin-like material. In cases of trachoma and inclusion conjunctivitis initial bodies (Lindner[69]) were described as appearing in the cytoplasm and were stated to be the form from which the elementary bodies develop. They are round and sharply defined and measure 0.6 to 10 millicrons in diameter. According to Lindner, initial bodies develop from a ring form and multiply by repeated division to form groups and clusters. In the later stage of development minute, red-staining elementary bodies appear inside the initial bodies. Residual bodies lie inside the cell inclusion (red with the Giemsa stain and blue with the Mallory stain). They are larger than the initial bodies, but as the elementary bodies become more numerous, they diminish correspondingly. In Lindner's opinion, they do not represent a phase in the growth of the virus; they are simply nuclear fragments, and not living organisms. The plastin-like mass is considered a degenerative product of the cell in response to the invading virus.

The chlamydozoa of von Prowazek[67] were not easily accepted as the causative agent in trachoma; many authorities explained them as colonies of micrococci, secretion granules or chromatin masses in the cells. Criticism of his theory was based on observations by Gutfreund, who noted chlamydozoa only in 47 of 106 cases. Their specificity was also questioned because of their presence in nontrachomatous diseases, such as follicular conjunctivitis (Römer), chronic conjunctivitis (Addario), blepharoconjunctivitis (Axenfeld[70]) and conjunctivitis vernalis (Lodato and Thierfelder). Heymann[71] found the chlamydozoa in 4 cases of gonococcic conjunctivitis in the newborn and expressed doubt that they represented living organisms or that they had any connection with the causation of trachoma. In the second article he corrected his previously expressed opinion and stated that these bodies represent a virus pathologic for monkeys.

Further criticism of the specific nature of these bodies was based on their presence only in the epithelial, and not in the subepithelial, layers and in the follicles, while trachoma typically involves the deeper layers. Their presence in sections was interpreted as their being stained granulations of mast cells. The observation of identical inclusions in trachoma and in nongonococcic ophthalmia gave impetus to the revival of Arlt's view that the two conditions are different stages of the same disease, and inclusion conjunctivitis was interpreted as trachoma of the newborn, a concept strongly opposed on the basis of the difference in the clinical pictures and the histologic structures of the two conditions. Greeff, the originator of the term trachoma bodies, changed his opinion because of the presence of the inclusions in conjunctival diseases other than trachoma and denied that they had any specificity for trachoma. Led by the same misconception that the morphologically identical inclusions appear only in trachoma and nongonococcic ophthalmoblennorrhea Herzog,[68] on the basis of cultivation experiments, expressed the opinion that gonococci show forms of involution (microgonococci) and the inclusions represent an aggregation of these forms, an opinion almost universally rejected by other investigators. The results of the cultivation experiments intensified the existing confusion. Schiele reported that he had produced chlamydozoa in pure culture (on ordinary mediums) in 34 cases and transmitted the disease from the culture by inoculation of dogs. Noguchi and Cohen,[72] similarly, reported positive results on culture. Later experience did not confirm these observations. Thygeson and Mengert[73] proved that cultivation was unsuccessful even on the chorioallantoic membrane of the chicken embryo, the classic culture medium of viruses. The question of transmission to animals, however, was settled, as it is possible to transmit the disease only to monkeys. The experiments with earthenware filtration usually gave negative, but sometimes contradictory, evidence, and the results could not be considered useful in classification until Thygeson and Proctor[74] proved that the virus passes through collodion membrane filters with an average pore diameter of less than 0.2 micron and therefore is readily filtrable. These experimental results were confirmed by Julianelle and Smith[75] and by Stewart. Research on the virus of trachoma, which received a special impetus

69. Lindner, K.: The Free Initial Form of Prowazek's Inclusion Bodies, Wien. klin. Wchnschr. **22**:1697 and 1742, 1909; Staining of Prowazek's Inclusion Bodies, Zentralbl. f. Bact. **57**:429, 1910; Biologic Relation Between Inclusion Virus of Trachoma and Bacterium Granulosis Noguchi, Arch. f. Ophth. **122**: 391, 1929.

70. Axenfeld, T.: Die Aetiologie des Trachoms, Jena, G. Fischer, 1914.

71. Heymann, B.: Sites of the Prowazek Bodies, Berl. klin. Wchnschr. **47**:663, 1910.

72. Noguchi, H., and Cohen, M.: Experiments on the Cultivation of the So-Called Trachoma Bodies, Arch. Ophth. **40**:1, 1911; **43**:117, 1914.

73. Thygeson, P., and Mengert, W. F.: The Virus of Inclusion Conjunctivitis, Arch. Ophth. **15**:377 (March) 1936.

74. Thygeson, P., and Proctor, F. I.: The Filtrability of Trachoma Virus, Arch. Ophth. **13**:1018 (June) 1935.

75. Julianelle, L. A., and Smith, L. E.: Studies of Infectivity of Trachoma, Am. J. Ophth. **22**:62, 1940.

from the discovery of similar inclusions in psittacosis, has shown that the inclusion bodies are always present in cases of untreated trachoma. The bodies are filtrable, and the disease can be transmitted to monkeys and apes, but without the formation of pannus or the typical cicatricial involvement which characterizes invasion of the human conjunctiva and the corneal epithelium. According to Perdrau,[76] the possibility exists that all forms of trachoma are not caused by one and the same virus, or strains of the virus, and that Egyptian and Brazilian trachoma may represent different strains of the same virus, each possessing fixed characters.

A different group of authors, which included Busacca,[77] Cuénod and Nataf [78] and Poleff, stated that the existing agent in trachoma is a rickettsial organism. Cuénod and Nataf [78] claimed they had successfully recovered rickettsial bodies from the intestine of lice experimentally infected with trachomatous material by the intra-anal route, and had transmitted the disease to a human volunteer by means of crushed lice infected with trachoma. The subject manifested allegedly typical trachoma sixty days after the onset of symptoms. Busacca, who noted inclusion bodies in the epithelial cells and follicles of trachomatous patients, concluded that the bodies were the causative agent and, accordingly, called them the rickettsias of trachoma. This was a premature conclusion, in view of the fact not only that Thygeson [79] was unable to confirm the findings, but that in his opinion, the so-called bodies represent only cell granules and protoplasmic debris. The rickettsial origin of trachoma was denied by Julianelle and Smith, [75] de Rõtth,[80] Braley [81] and Bengston,[82] and the louse cannot be regarded as the vector in trachoma.

Bacillus granulosis, described by Noguchi in 1927, was proved not to be the cause of trachoma, but only the etiologic agent in folliculosis of the conjunctiva.

The inclusion bodies of trachoma were observed in two other conjunctival diseases, namely nongonococcic blennorrhea of the newborn and swimming pool conjunctivitis. The inclusion bodies with basophilic cytoplasm had already been discovered by Halberstaedter and von Prowazek [66] in cases of nongonococcic ophthalmoblennorrhea after careful bacteriologic examination had excluded the presence of gonococci. Shortly afterward, Heymann discredited the importance of the discovery by stating that the inclusion bodies are present in gonococcic infection of the conjunctiva, and he consequently explained their presence as a cellular reaction due to the gonococci. Conversely, Stargardt emphasized that the inclusion bodies were present only in the absence of gonococci. Wolfrum and Lindner observed inclusion bodies constantly in nongonococcic conjunctivitis and could not prove their presence in the gonococcic form. These observations, corroborated by other authors, were instrumental in establishing inclusion blennorrhea (inclusion conjunctivitis) as a separate clinical entity, characterized by a milder course than that of gonococcic conjunctivitis, the secretion being much less in amount and rather serous. Furthermore, inclusion conjunctivitis was associated with an almost constant absence of corneal complications and by a longer period of incubation (in adults, seven to ten days, and in the newborn, five to nine days). Lindner succeeded in identifying the inclusion bodies in the urethra, and even in the vagina, in cases of urethritis of nongonococcic type. Lindner, Fritsch and Hofstadter produced trachoma-like changes in Macacus rhesus monkeys and in baboons through inoculation of the secretion. Morax and Bollack, Nicolle, Cuénod and Blaizot and Botteri and Leber confirmed the transmission of inclusion conjunctivitis to monkeys, even by means of material passed through a Berkefeld filter. The inclusion urethritis of the male and the inclusion cervicitis of the female became recognized as clinical entities in certain countries. But

76. Perdrau, J. R.: Virus Infections in Ophthalmology, in Ridley, F., and Sorsby, A.: Modern Trends in Ophthalmology, New York, Paul B. Hoeber, Inc., 1940, p. 32.

77. Busacca, A.: Frequency of Corneal Complications in Trachoma, Rev. internat. du trachome **10**:57, 1933; Structure of Herbert's Pits, Compt. rend. Soc. de biol. **117**:715, 1934; Brit. J. Ophth. **19**:26, 1935; Anatomicopathologic and Clinical Observations on Pannus Trachomatosus of the Cornea, Arch. Ophth. **11**:730 (April) 1934; Is Trachoma Rickettsial Disease? ibid. **17**:117 (Jan.) 1937.

78. Cuénod, A., and Nataf, R.: Le trachom, Paris, Masson & Cie, 1930; Contagiosity of Trachoma, Arch. d'opht. **50**:261, 1933; Possible Role of Rickettsia in Causation of Trachoma, ibid. **53**:355, 1936; Bacteriological and Experimental Researches on Aetiology of Trachoma, Brit. J. Ophth. **21**:309, 1937; Experimental Trachoma, Ann. d'ocul. **174**:433, 1937; Etiology and Pathogenesis of Trachoma, Rev. internat. du trachome **14**:117, 1937.

79. Thygeson, P.: Microbic Etiology of Trachoma, Arch. Ophth. **11**:728 (April) 1934; Nature of Elementary and Initial Bodies of Trachoma, ibid. **12**:307 (Sept.) 1934; Biomicroscopy of Limbus Corneae in Trachoma and Other Conjunctival Disease, Am. J. Ophth. **17**:787, 1934.

80. de Rötth, A.: Problem of Etiology of Trachoma, Arch. Ophth. **22**:533 (Oct.) 1939.

81. Braley, O. E.: Rickettsial Question in Trachoma, Arch. Ophth. **22**:262 (Aug.) 1939.

82. Bengston, I. R.: Question of Rickettsial Nature of Trachoma, Am. J. Ophth. **23**:770, 1940.

the condition is comparatively rarely diagnosed, either because the patient does not seek medical attention, owing to the mildness of the symptoms, or because the disease escapes detection. Thygeson and Mengert [73] reported the case of a gynecologist who was infected in performing a dilation and curettement and in whom conjunctivitis developed six days later, the secretions showing free initial and elementary bodies. After observation of the inclusions in the male urethra. Lindner stated that the two viruses were identical and referred to the virus of inclusion conjunctivitis as the virus of paratrachoma. Inclusion conjunctivitis and inclusion urethritis heal without producing general immunity or neutralizing antibodies in the serums. Botteri and Gebb found the virus capable of passing through the pores of earthenware filters; Thygeson, using an Elford collodion membrane of 0.6 micron pore diameter, observed the individual elementary body, of 0.25 micron diameter, in stained specimens, the initial body being 0.3 to 0.8 micron in diameter.

Morphologically the virus of trachoma and the virus of inclusion blennorrhea (including swimming pool conjunctivitis) cannot be differentiated. Biologically it is possible that they are variants of the same virus, in anology with the virus of variola and vaccinia. Virus research has resulted in the identification of a new clinical entity, nongonococcic inclusion conjunctivitis. Swimming pool conjunctivitis, often unilateral and similar to inclusion conjunctivitis, but without pannus formation or cicatrization, is due to the same virus, infection probably taking place through contamination of stagnant water with urine of patients with inclusion urethritis. The inclusion conjunctivitis of the newborn is usually bilateral; in cases of unilateral infection the second eye becomes involved after six days or more. When pseudomembranes form, the possibility of scarification exists, as pointed out by Lindner, Aust and Lombroso, not as a result of an inherent tendency to scarring but as a sequel to the intense inflammatory process. Clinically there are changes of the follicular or papillary type, with adenopathy.

HERPES SIMPLEX

Long before the discovery of the virus origin of herpetic diseases, which afforded differentiation of the virus of herpes simplex febrilis (corneae, cutis and genitalis) and that of herpes zoster, clinical ophthalmology had achieved a differentiation of these two forms of corneal lesions. In herpes febrilis the vesicular eruption, often accompanied by symptoms of involvement of the respiratory tract, is of short duration and clears up without dense cicatrization. Conversely, the eruption of the cornea in herpes zoster, a sequel to infection of the nasociliary branch, is characterized by long duration, involvement of the stroma of the cornea, severe iritis and formation of deep and dense scars.

The clinical picture of herpes febrilis corneae was clearly outlined by Horner,[83] in 1871, and his pupils Haab, Kendall, Wangler and Hagnauer subsequently defined it in minute detail. Other authors have proposed a different nomenclature for herpetic disease of the cornea: Keratitis dendritica myotica exulcerans (Emmert); kératite ulcéreuse en sillon étoilée (Gillet de Grandmont), and keratitis ramiformis (Hansen and Grut) are examples, but these terms have not been accepted.

In 1873 Vidal demonstrated that herpes was infective, but little interest was taken in this fact until Grueter [84] produced herpes simplex in the cornea of the rabbit, proving the existence of a virus or virus-like agent and disproving the previously accepted theory of a trophic disturbance of the trigeminal nerve. The discovery of the transmissibility of the disease should doubtless be accredited to Grueter. Some authors have cited Loewenstein [85] or Loewenstein and Grueter. Loewenstein published his work before Grueter's and mentioned only briefly the latter's transmission of herpes to the cornea of the rabbit. Grueter achieved this in 1912, and his work represents the first clear positive evidence of the causation of herpes. He reported positive results from inoculation of the scarified cornea of the rabbit with material from a case of dendritic keratitis, passage from rabbit to rabbit and reinoculation from rabbit to man, and he noted that the inoculated animals were immune to revaccination with herpes. These observations were confirmed and extended to include all the varieties of herpes of the skin (Loewenstein) exclusive of herpes zoster. Forty-eight hours after the inoculation the scarified rabbit cornea revealed cloudiness with numerous small focal swellings. In the next two days purulent conjunctivitis and ulceration of the cornea became manifest. The local inflammation subsided in a few days, with residual corneal

83. Horner: Herpes Zoster Corneae and Herpes Febrilis Corneae, Klin. Monatsbl. f. Augenh. **9**:172, 1871.

84. Grueter, W.: Experimental and Clinical Studies of So-Called Corneal Herpes, Klin. Monatsbl. f. Augenh. **65**:398, 1920; The Herpes Virus and Its Clinical and Etiologic Significance, München. med. Wchnschr. **31**:1058, 1924.

85. Loewenstein, A.: Experimental Studies on Virus of Herpes Febrilis, Klin. Monatsbl. f. Augenh. **64**:15, 1920.

damage of variable degree. The scarified cornea of the rabbit became the classic culture medium for the inoculation of viruses. Only recently, Gallardo [86] reported that transmission is possible without mechanical insult to the corneal epithelium, by dropping or swabbing the material into the conjunctival sac. A later observation by Doerr proved that after nine days a certain proportion of the inoculated animals showed a lesion of the central nervous system, which manifested itself in forced turning to the infected side, paralysis of the rear extremities, convulsions and death. The route of extension after inoculation of the cornea is the retina, the optic nerve and the sensory divisions of the fifth and ninth nerves. The virus proved to be transmissible from rabbit to rabbit by the corneal or the intracerebral route.

In the early stage examination of the filtrations revealed no inclusions in the infected cells similar to Guarnieri bodies. This observation was contrary to the conclusion of Lipschütz [87] that the herpes virus was filtrable and belonged to the group of chlamydozoa and his report of numerous round, homogeneous and sharply outlined inclusions which filled the nucleus in the infected cells of the cornea. The inclusions were noted not only in the epithelial cells but in the fixed cells of the stroma, their presence denoting a nucleotropism of the virus. In Lipschütz' opinion, the inclusions represented reaction products of the cells to the invasion of the virus and belonged to the karyo-oikon group of chlamydozoa or strongyloplasms. The acidophilic nuclear inclusions occur in the epithelial cells of the cornea and skin. According to Goodpasture and Teague, they exist in all susceptible tissues of the infected animals. Nicolau and Kopciowska [88] concluded that the inclusion body was a closely packed colony of virus particles, not quite filling out the area rendered vacant by the peripheral accumulation of the chromatin. In rabbits, guinea pigs and mice, the central nervous system, next to the cornea, is most susceptible to the virus; however, other tissues are susceptible to a lesser degree, and cutaneous lesions can be produced by suitable strains. The external surface of the respiratory membrane (chorioallantois) of the developing chick embryo is covered by ectodermal epithelium and reacts to the virus, but mesodermal tissues can be inoculated, too (testicular inoculation of rabbits). The virus can be preserved in neutral glycerin. The brain of infected animals contains the virus, and transmission from brain to brain is possible. The virus is quantitatively the same in all herpetic eruptions and is present in the serum and the spinal fluid of patients with herpes, in the saliva of patients with and without herpes and occasionally in the spinal fluid of persons who have not recently had herpes of encephalitis (Flexner).

The herpes virus has an ectodermal affinity, is relatively large, being 0.1 micron in diameter in filtration products (Elford, Perdrau and Smith [89]) or 0.1 to 0.3 micron in Levaditi strains, and filters with relative ease, particularly when suspended in broth. The filtrability was first proved by Luger and Landa,[90] in 1921. The various strains of the virus differ in virulence. The virus shows adaptation to animal species and to special tissues. Doerr suggested that the herpes virus may be identical with the virus of encephalitis.

Recovery from corneal or cutaneous inoculation in rabbits results in immunity for six months or longer; the serum and, to a lesser degree, the brain tissue show limited and irregular neutralizing power. In animals the herpes represents a typical virus infection, an extrinsic infectious agent producing the effect in susceptible animals and in susceptible tissues. It is a qualitatively identical agent, which is transmissible indefinitely. In man the condition is less clear, and Doerr expressed the opinion that it is not an exogenous, but an endogenous, infection, arising from the reaction of products of the cells to a virus-like agent under the influence of physiologic stimuli. Once the agent is produced, it will act on the cells as a true virus, but is only a derivative of the physiologically modified human cell.

Burnet and Williams,[91] who did not accept Doerr's explanation, undertook to prove the exogenous nature of herpetic infections, as having a direct origin in a preexisting virus. The virus remains latent after disappearance of the clinical symptoms, but it may become activated under the stimulus of trauma or fever and produce new lesions. The fact that herpetic lesions tend to recur at the same sites (lip, finger and cornea) points to the presence of vegetation in the affected cells, but certain investigators have stated the opinion that the virus persists in some part

86. Gallardo, E.: Primary Herpes Simplex Keratitis, Arch. Ophth. **30**:217 (Aug.) 1943.

87. Lipschütz, B.: Chlamydozoa-Strongyloplasms, Wien. med. Wchnschr. **71**:231, 1921.

88. Nicolau, S., and Kopciowska, L.: Morphology of Herpetic Infrabacteria in Tissues of Experimentally Infected Animals, Ann. Inst. Pasteur **60**:401, 1938.

89. Elford, W. J.; Perdrau, J. R., and Smith, W.: The Filtration of Herpes Virus Through Graded Collodion Membranes, J. Path. & Bact. **56**:49, 1933.

90. Luger and Landa: Etiology of Herpes Febrilis, Ztschr. f. d. ges. exper. Med. **24**:289, 1921.

91. Burnet, F. M., and Williams, S. W.: Herpes Simplex: A New Point of View, M. J. Australia **1**: 637, 1939.

of the nervous system, perhaps in the Gasserian ganglion, or in the mouth or the salivary glands.

Herpes is an acute disease of infancy and early childhood, 90 per cent of the population showing herpetic antibodies, which in all probability prevent the occurrence of herpetic stomatitis later. Gundersen's [92] observation, based on 250 attacks of herpes in 225 patients, that the incidence of the disease was highest before the tenth year of life seems to be in accordance with that of Burnet and Williams, who expressed the belief that herpes is a disease of early childhood. In my experience, dendritic keratitis in childhood is extremely rare, and in adults recurrence is always in the same cornea, a characteristic which apparently excludes the presence of virucidal antibodies. Gallardo's [86] examinations showed that in cases of primary herpes of the cornea the serum did not contain neutralizing antibodies in the early stage (at the end of two or three days in 4 of 5 cases). In 17 cases of corneal herpes with a history of previous corneal or cutaneous eruptions, the antibodies were present at the onset. The recurrence of herpetic lesions in spite of the presence of neutralizing antibodies points to the persistence of the virus within the susceptible cells. The virus of herpes and that of epidemic keratoconjunctivitis are further differentiated by the long duration of the corneal manifestations in the latter disease and by the absence of a tendency to recur. It should be mentioned briefly that Gundersen had 63 positive results in 180 inoculations and that in 3 cases the picture was that of disciform keratitis.

It is interesting to note that the neurotropic quality of the herpes virus led von Szily [93] to study sympathetic ophthalmia. He produced inflammation of the second eye in rabbits, but in 20 per cent of the animals the inoculation resulted in severe encephalomeningitis. Similar experiments were undertaken by Gifford and Lucie [94] and by Velhagen [95] but the results can be considered only as transmission of the virus infection to the second eye, without its being connected with the causation of sympathetic ophthalmia in man. In sympathetic ophthalmia the histologic picture is compatible with, if not suggestive of, a virus origin. While the presence of mononuclear elements, with a thick cuff around the vessel, testifies to a virus origin, the presence of eosinophilia points, rather, to an allergic factor.[76]

92. Gundersen, T.: Herpes Corneae, Arch. Ophth. **15**:225 (Feb.) 1936.

93. von Szily, A.: New Paths in the Experimental Research of Sympathetic Ophthalmia, Deutsche med. Wchnschr. **52**:1598, 1926.

94. Gifford, S. R., and Lucie, L. M.: Sympathetic Uveitis Caused by the Virus of Herpes Simplex, Tr. Sect. Ophth., A. M. A., 1926, p. 20.

95. Velhagen, K.: Experiments with Herpes Virus on Transmission of the Infection from One Eye to the Other, Arch. f. Ophth. **119**:324, 1927.

HERPES ZOSTER

Herpes zoster, in its primary and secondary (symptomatic) form, is probably due to the same virus as that of herpes febrilis, the spread of the virus being distal, along the distribution of the nerve.

The virus of herpes zoster has not been as extensively studied as that of other viruses, owing to lack of susceptible experimental animals. The virus is possibly identical with, or at least closely related to, that of varicella, herpes zoster being the dermotropic and varicella the neurotropic manifestation of the same virus. Thygeson,[16] in his exhaustive review, summarized the similarities of varicella and herpes zoster and mentioned the identity of the incubation periods and the cross agglutination and complement fixation reactions, the similarities in the histologic changes and in the inclusion and elementary bodies, the nontransferability and noncultivability of the viruses, the lasting immunity produced by both and the resemblance of the clinical pictures and the occasional simultaneous occurrence of the two conditions.

MOLLUSCUM CONTAGIOSUM

Molluscum contagiosum was first described by Bateman, in 1817. Long before viruses were recognized, the large hyaline structures in the lesions of molluscum contagiosum, now identified as inclusion bodies, were described almost simultaneously by Henderson [96] and by Paterson [97] in 1841. The filtrable acidophilic cytoplasmic inclusions, which are microscopically visible, consist of an aggregation of minute elementary bodies; they were first described by Lipschütz,[98] who called them Strongyloplasmas, because viruses of this type are manifest as delicate, round bodies. According to Lipschütz, Strongyloplasma hominis is the virus responsible for molluscum contagiosum. The elementary body is 0.25 micron in diameter in Giemsa-stained films and is embedded in a matrix containing lipid elements. The inclusion body is circular or pear shaped and is surrounded by a membrane. Van

96. Henderson, W.: Notice on the Molluscum Contagiosum, Edinburgh M. & S. J. **56**:213, 1841.

97. Paterson, R.: Cases and Observations on the Molluscum Contagiosum of Bateman, with an Account of the Minute Structure of the Tumours, Edinburgh M. & S. J. **56**:279, 1941.

98. Lipschütz, B.: Diagnosis of Molluscum Contagiosum, Wien. klin. Wchnschr. **20**:253, 1907; footnote 17.

Rooyen and Rhodes[99] demonstrated that the inclusion body can be removed from the cell by microdissection and that the capsule contains glycogen. The virus passes the Chamberland, Berkefeld, Berkefeld V and Pasteur-Chamberland L filters. The serum from patients with the disease contains no agglutinins, the absence of which may be attributed to the fact that the virus grows only in the superficial epithelial layers. That the virus is not transmissible to laboratory animals, not even to Macacus rhesus monkeys, suggests a high specificity of the virus with respect to species and tissue. Julianelle and James[100] confirmed the nontransferability of the virus to monkeys, rabbits and mice (by the intraperitoneal and the intracerebral route in the latter), but implantation in hens' eggs was followed in 2 out of 4 instances by infection of the chorioallantoic membrane, multiplication of the virus and the appearance of inclusion bodies.

Cutaneous transmission of molluscum contagiosum from man to man has been accomplished. The virus origin was established in 1905 by Juliusberg,[101] who demonstrated the transmissibility by material passed through Chamberland filters. The period of incubation after inoculations of filtered or unfiltered tissue extract varies from fourteen to fifty days, according to different authors. The inclusion bodies originally were thought to represent a parasitic protozoon (Lipschütz, von Prowazek). The virus does not produce immunity. The ocular manifestations are nodules on the margins of the lids; a follicular or, rarely, a papillary form of conjunctivitis; keratoconjunctivitis, with subepithelial infiltrates resembling the epidemic variety,[102] and actual tumor of the conjunctiva, or even of the cornea.

99. Van Rooyen, C. E., and Rhodes, O. J.: Virus Diseases of Man, London, Oxford University Press, 1940.

100. Julianelle, L. A., and James, W. M.: Molluscum Contagiosum of the Eye: Its Clinical Course and Transmissibility and Cultivability of the Virus, Am. J. Ophth. **26**:565, 1943.

101. Juliusberg, M.: Virus of Molluscum Contagiosum in Man, Deutsche med. Wchnschr. **31**:1598, 1905.

WART (VERRUCA VULGARIS)

Conjunctivitis, superficial keratitis and, in 1 case, a catarrhal type of ulcer were described by de Rötth[103] as complications of wart, with a tendency to heal promptly after removal of the lesion. The infectivity of warts was first proved by Variot and Jadassohn, and the filtrability of the virus through a Berkefeld N candle filter was demonstrated by Ciuffo, in 1907. Later, investigators found the virus filtrable through Berkefeld filters of all grades of porosity.

The spreading of warts by bleeding has long been known to the laity, before the infectivity was established scientifically. Despite numerous attemps, animal inoculations yielded definite results only with the transmission of laryngeal papilloma. Elementary bodies were not described. The increased eosinophilic granularity of the superficial layers often led to their being described as inclusion bodies. The inclusion bodies were said to be basophilic or eosinophilic, cytoplasmic or nuclear. Large granular eosinophilic bodies have been described by various authors, but their presence cannot be considered as proved, and further investigation is required. The nuclear inclusions are likewise questionable. The virus has not been cultivated.

31 Lincoln Park.

102. Lee, O. S.: Keratitis Occurring with Molluscum Contagiosum, Arch. Ophth. **31**:64 (Jan.) 1944.

103. de Rötth, A.: Common Wart as an Etiologic Factor in Certain Cases of Conjunctivitis and Keratitis, Arch. Ophth. **21**:409 (March) 1939.

Correspondence

ANTERIOR PERIPHERAL SYNECHIAS IN EXPERIMENTAL ACUTE GLAUCOMA

To the Editor:—In his interesting paper entitled "Development of Anterior Peripheral Synechiae in Experimental Acute Glaucoma" (ARCH. OPHTH. 31:481 [June] 1944), Dr. M. Uribe Troncoso compares the formation of peripheral synechia in experimental glaucoma produced by injection of serum or pure or defibrinated blood into the anterior chamber of animal eyes with the acute glaucoma of human eyes. He concludes that experiments with animals show that the first step in the production of this increase in tension was not the mechanical obstruction of the channels of outflow by the base of the ciliary body and the root of the iris but a disturbance in the normal outflow of aqueous. These conclusions cannot be applied to the condition designated as acute glaucoma in man. In the latter condition there is an anatomic predisposition, namely, shallowness of the anterior chamber, which is always present. In the animal eyes studied by Dr. Troncoso the chambers were normal. I believe that this experimental condition might be compared more appropriately to the development of peripheral anterior synechias in certain cases of so-called secondary glaucoma associated with inflammatory increase of protein in the aqueous, but not to acute glaucoma.

Dr. Troncoso also states in his conclusions that the "thickened processes pushed the root of the iris forward, made the anterior chamber shallow and produced an anterior peripheral synechia." This process cannot be compared to human acute glaucoma, in which there is no evidence of any decrease in depth of the anterior chamber before or after the attack. It is true that edema of the ciliary body and the root of the iris decrease the angle, but not the axial depth, of the anterior chamber.

In the early part of his paper Dr. Troncoso refers to my previous work as reviving the theory that mechanical occlusion of the angle by peripheral synechias is the principal cause of acute glaucoma. This statement may cause misunderstanding, since I have always considered that peripheral synechia is secondary and that simple mechanical occlusion by approximation of the iris to the trabecula is the primary cause of the increased intraocular pressure in acute glaucoma. Peripheral synechias form only afterward, when edema and exudation from the ciliary body are present, during the congestive phase of this condition.

Again, Dr. Troncoso refers to my series of 20 eyes with shallow angles, in 6 of which mydriasis produced acute glaucoma, and states that in the 14 eyes in which mydriasis did not cause increased tension "the mydriatic did not produce any hypertension, although the dilation of the pupil undoubtedly narrowed the entrance to the chamber recess." In that paper (Sugar, H. S.: The Mechanical Factors in the Etiology of Acute Glaucoma, *Am. J. Ophth.* 24:851, 1941) I pointed out that the angle cannot be blocked unless the combination of thickness of the iris, amount of dilation and shallowness of the angle is sufficient to produce mechanical blocking. Simple narrowing of the entrance is not enough. Mydriasis in that series of cases was not sufficient to produce the desired mechanical effect.

MAJOR H. SAUL SUGAR, Medical Corps,
Army of the United States.

To the Editor:—In his letter Major H. Saul Sugar disagrees with some of my conclusions and objects to some of the interpretations I advanced as a result of my experimental work. Hence I consider it necessary to make certain explanations and to clarify my point of view.

Dr. Sugar states that my experiments on animals "cannot be applied to the condition designated as acute glaucoma in man because in man there is an anatomic predisposition, namely, shallowness of the anterior chamber, "which is always present, [while] in all animal eyes studied the chambers were normal." From the beginning I clearly stated in my paper that, unfortunately, there is as yet no means of reproducing experimentally the symptom complex designated as acute primary glaucoma in man. The injection of serum or pure or defibrinated blood into the anterior chamber is, in my opinion, the more physiologic approach to the experimental production of a sudden and great increase in intraocular pressure. Once this increase has developed, it is possible to ascertain the time of onset, the origin and the mechanism of formation of anterior peripheral synechia.

Dr. Sugar states that an indispensable condition for the production of acute glaucoma is "always" a predisposing factor, shallowness of the anterior chamber. I believe that even in man this is not always a requirement for development of the acute attack. One of the most important contributions to ophthalmology made by gonioscopy has been to prove beyond doubt that a high intraocular pressure may coexist with an entirely open angle. I have described cases of glaucoma in which a tension of 40 mm. of mercury or more coexisted with an entirely open angle and an anterior chamber of normal depth. These observations discredit the old theory of Knies

and Weber that the *primum movens* in the causation of hypertension is always the mechanical application of the root of the iris to the corneoscleral limbus.

It is well known that subacute, or even acute, attacks may develop suddenly in eyes affected with simple glaucoma. It has been objected that in such cases acute hypertension, and not acute glaucoma, was the condition involved. Dr. Sugar and other observers assert that an acute attack may be present without any symptoms of congestion and that congestion is not the characteristic feature of the acute exacerbation. This opinion is contrary to that of the majority of ophthalmologists. Periodic elevations of the intraocular pressure may exist with no congestion in cases of simple glaucoma, but when a true attack develops there is always a sudden and great increase of the pressure inside the eye. This compresses the intraocular veins, especially the venae vorticosae, and gives rise to congestion and secondary edema of the ciliary body and ciliary processes. The swollen processes compress the root of the iris against the trabeculum, so that the channel of outflow for the intraocular fluid is mechanically closed and thus another factor is added to the already high pressure.

Which condition is the cause of the primary, sudden elevation of tension in the acute attack is not yet known, but it can be stated that when the causative factor is not sufficiently strong the attack is slight or prodromal. In cases of this type, the channels of outflow being normal, the level of tension falls quickly to normal, even when there is shallowness of the angle and the volume of the lens is probably greater. I have ascertained by gonioscopic examination that after a prodromal attack the angle of the anterior chamber remains open, either totally or partially. When the exciting factor is stronger and raises the intraocular pressure suddenly to a high level, inflammatory edema soon appears. The swollen processes compress the root of the iris against the sclera and produce an anterior peripheral synechia.

Dr. Sugar states that in the acute attack in man "there is no evidence of any decrease in depth of the anterior chamber before or after the attack." This opinion is opposed to the accepted view. Dr. Sugar probably supports this assertion by his direct measurements of the depth of the chamber. These, however, have not yet been confirmed. At any rate, he concedes that the edema of the ciliary body and the root of the iris makes for shallowness of the angle, which is the important point.

He fears my contention that he and other observers consider the mechanical closing of the angle by peripheral synechia as the first step and the principal cause of the acute attack may lead to misunderstanding of his position. He adds that simple mechanical occlusion "by approximation" of the iris to the trabecula is the primary cause of increased intraocular pressure. These two statements differ only in their wording. The majority of ophthalmologists consider the application of the root of the iris to the trabecula as a peripheral synechia. This application, or agglutination, may be temporary if the iris is detached by the use of a myotic, or it may become permanent if the two membranes are bound together by connective tissue. The word "approximation" is misleading. It is only when the root of the iris comes in direct contact with the trabecula and covers it entirely that the channel of outflow is blocked. Dr. Sugar himself states later that "simple narrowing of the entrance of the chamber is not enough . . . the angle cannot be blocked unless the combination of thickness of the iris, amount of dilation of the pupil and shallowness of the angle is sufficient to produce mechanical blocking." I am entirely in agreement with him on this point. I merely indicated that in only 6 of his series of 20 eyes with shallow angles were these conditions met with and mydriatic glaucoma produced, while in the other 14 eyes the mydriatic did not give rise to elevation of tension. In my opinion, while mechanical blocking of the angle may "start" the cycle of symptoms of acute hypertension in some cases, in the majority the initial cause of the acute attack should not be ascribed to the mechanical occlusion of the angle of the anterior chamber.

I stated in my paper that while the anatomic differences between the angle of lower mammals and that of man are great, the experimental production of a sudden increase in tension was usually accompanied by congestion of the eye, edema of the conjunctiva and chemosis. In monkey eyes, the anatomic features of which are similar to those of the human eye, the same symptoms were produced. My aim was to determine the reaction of the eye to experimental hypertension of a high degree, to ascertain whether the anterior peripheral synechia was immediately or secondarily produced and, in the latter case, to determine the mechanism of its development.

I am obliged to Dr. Sugar for bringing this important subject under discussion.

MANUEL URIBE TRONCOSO, M.D.,
New York.

630 West One Hundred and Sixty-Eighth Street.

Obituaries

SIR WILLIAM LISTER, M.D.

1868-1944

Sir William Lister died at his home in High Wycombe, Buckinghamshire, England on July 7, 1944. He was born on Nov. 4, 1868, the youngest son of Arthur Lister, F.R.S., an eminent botanist, and was a nephew of the great Lord Lister. He attended Cambridge University and then received his medical education at the University College Hospital, in London, and at Cambridge, where he graduated in 1892 and obtained the F.R.C.S. diploma in 1895. He was early drawn to ophthalmology, and he began work under Sir John Tweedy at Moorfields. Like so many eminent predecessors, Lister was curator of the pathologic museum at Moorfields before being elected to the visiting staff there. He also acted as ophthalmologic surgeon to the London Hospital. In 1914, at the onset of the first world war, he was asked to take charge of the ophthalmic arrangements for the Expeditionary Force in France. Mr. Charles Goulden, in the August 1944 issue of the *British Journal of Ophthalmology* states that "the task of organizing the ophthalmic service of the British Armies in France" was an arduous one, but "by his persistence he ultimately overcame all difficulties and set up a most successful organization whereby not only was there an ophthalmic consultant available for each Army but surgical aid was obtainable at certain casualty clearing stations. . . ." His organization "was a great triumph, and it was achieved in the face of much opposition."

After the termination of the war Lister returned to the staff at Moorfields, where he became an active and most successful teacher in the training of postgraduates in ophthalmology. In 1918 he gave a Hunterian Lecture before the Royal College of Surgeons on war injuries of the eye. Lister published important papers on interstitial keratitis, on retinal holes and on mustard gas burns of the eye. He was one of the first to discover that in retinal detachment the vitreous is always shrunken from one-third to one-half its former size, and in his paper on detachment of the vitreous, read before the International Congress of Ophthalmology in Washington, D. C., in 1922, he drew attention to holes in the vitreous. He made several improvements in the instruments in constant use by ophthalmologists, and of these his perimeter was the most important.

He and Lady Lister were much interested in the Moorfields Eye Hospital and, in addition to other bequests, made a large donation for a convalescent home. At the English-speaking Congress in London in 1928 the American visitors will always remember the garden party given by Sir William and Lady Lister at the home of the Misses Alexander in South Kensington. In 1934 he was chosen consulting ophthalmologic surgeon to the King.

A man of the highest principles, of a modest and generous nature, Lister will long be remembered as a great clinician, a fine operator and an excellent teacher.

The material for this obituary was obtained from the *British Medical Journal* (**2**: 130 [July 22] 1944) and from the *British Journal of Ophthalmology* (**28**:424 [Aug.] 1944).

ARNOLD KNAPP.

Abstracts from Current Literature

EDITED BY DR. WILLIAM ZENTMAYER

Aqueous Humor

A CASE OF CAVERNOUS SINUS THROMBOSIS. P. D. TREVOR-ROPER, Brit. M. J. **1:** 255 (Feb. 19) 1944.

A boy aged 14 years struck the region of his left eyebrow on a door handle. Two days later, as the area became sore, he attended the hospital, but nothing was apparent except a slight abrasion of the skin. The following day the eye began to protrude, and he had a temperature of 103 F. The condition rapidly grew worse; on the following evening the other eye was equally proptosed, and the next day the whole face was swollen. He was then vomiting, was incontinent and became semicomatose. This condition lasted one week, with the temperature about 103 F.; he then gradually recovered. On the fifth to the eighth day tremors affected all the muscles of the face and the arm on one or both sides. The only changes in the fundus were slight engorgement of the retinal veins and possible blurring of the margin of the left optic disk. On his return to consciousness there was paralysis of the left side of the face which cleared in about a fortnight. There were stiffness of the right leg and paresis of the left external rectus muscle, which disappeared in a few days. Convalescence was delayed by mild basal pneumonia and a small subcutaneous orbital abscess. Vision was 6/5 in each eye.

Treatment included the administration of sulfapyridine, which could be given only intramuscularly after the second day, and then oral use of sulfadiazine, 32 Gm. the first week and 21 Gm. the second week. Administration of 4 pints (1,890 cc.) of 5 per cent dextrose in isotonic solution of sodium chloride, given as drip transfusions, was necessary while he was incontinent, vomiting and unable to take fluids by mouth.

In 1936 cavernous sinus thrombosis had a 100 per cent mortality. Since the advent of sulfonamide compounds, cures have been reported in 12 cases. In 3 cases, in conjunction with sulfathiazole, heparin was used for the prevention of extension of the clotting; in addition, staphylococcus antitoxin is recommended, even when the blood culture is sterile.

The author believes that the infection in this case reached the orbit from a nasal sinus through a fracture of the intervening bone, although this could not be shown on roentgenographic examination. (The abrasion of the brow was quite sufficient to serve as a portal of entrance for the infection and was a much more probable source than the nasal sinus [abstracter].) The meningeal irritation and residual palsies are a frequent accompaniment. Retinal changes have rarely been severe in the cases in which recovery occurred.

ARNOLD KNAPP.

Congenital Anomalies

COLOBOMA OF THE OPTIC NERVE: REPORT OF A CASE. T. STEINBERG, Am. J. Ophth. **26:** 846 (Aug.) 1943.

A man aged 20 had visual acuity of 6/60 in the left eye, which was unimproved by a correction of — 1 D. sph. ⌒ — 1 D. cyl., axis 55. There appeared to be a pseudo optic disk, about three times the size of the normal disk. Its center was conspicuously excavated, from — 6 to — 8 D.

The central portion was bluish gray and the periphery grayish white. The margins were sharply defined, the temporal side showing a thin, irregular ring of choroid pigment. The vessels appeared to emerge at the borders and bend sharply at the edges, corresponding to group 3 of Caspar's classification. No other lesions were present. The nasal field showed slight peripheral contraction and decided enlargement of the blindspot.

W. ZENTMAYER.

Cornea and Sclera

THE PIGMENT OF THE KAYSER-FLEISCHER RING. R. E. ECKARDT, I. H. STOLZAR, A. B. ADAM and L. V. JOHNSON, Am. J. Ophth. **26:** 151 (Feb.) 1943.

The authors give the following summary:

"1. Two cases of Wilson's disease, with typical Kayser-Fleischer rings in the corneas, are reported. A brief case history of each is given.

"2. The ashed corneas from these cases were subjected to spectrographic analysis. Abnormal cations common to both cases were zinc, copper, and iron. In addition, the cornea in one case showed the presence of silver and aluminum.

"3. No conclusions are drawn from these analyses, other than that the pigment deposited in the cornea in Wilson's disease may vary from case to case, even though showing certain similarities, and that this pigment may be more complex, at least in its cation composition, than was heretofore believed."

W. S. REESE.

CLEARING OF EDEMATOUS CORNEAS BY GLYCERINE. D. G. COGAN, Am. J. Ophth. **26:** 551 (May) 1943.

Cogan has found the use of glycerin especially useful in examining patients who come to the clinic for the first time with acute attacks of glaucoma and in whom the steaminess of the cornea prevents adequate examination of the eye. If the cornea again becomes steamy, drops of glycerin may be instilled several times. The clearing effect lasts less than five minutes. He has found it to last longer if glycerin is used in tablet form. Glycerin tablets may be obtained by cutting up infant suppositories into appropriate sizes.

W. ZENTMAYER.

Experimental Pathology

THE REACTION OF THE RABBIT EYE TO NORMAL HORSE SERUM: SENSITIZATION BY INTRADERMAL INJECTION. T. F. SCHLAEGEL JR. and J. B. DAVIS, Am. J. Ophth. **26:**785 (Aug.) 1943.

Schlaegel and Davis summarize their article and draw the following conclusions:

"Signs of uveitis were seen after 24 hours in the right eye of every rabbit previously sensitized by intradermal injection but were absent almost uniformly from the eyes of the control group.

"The uvea was the most involved membrane. It was infiltrated with lymphocytes, multinucleated giant cells, epithelioid-like cells, large mononuclears, and plasma cells.

"On the internal surface of the retina there developed an astrocyte type of gliosis that produced an additional inner layer almost as thick as the retina itself.

"Cellular infiltration in the control animals was less intense but of the same type as in those of series 1. It did not appear until 14 days had elapsed, but was constant thereafter.

"The histopathologic results of 'staphylodiphtheroid antigen' have been duplicated roughly by using normal horse serum.

"The microscopic picture obtained in the eyes injected with normal horse serum bears a close resemblance to that of sympathetic ophthalmitis."

W. ZENTMAYER.

General Diseases

SEVERE KERATO-IRITIS DUE TO BRUCELLOSIS: SUCCESSFUL TREATMENT WITH BRUCELLA ABORTUS VACCINE. J. GREEN, Am. J. Ophth. **26:** 491 (May) 1943.

Green is convinced that brucellosis is the true etiologic factor in many inflammatory ocular diseases. He cites the case of a young woman of rather low mentality who had well developed iritis, with subsequent deep vascular keratitis, in the right eye. The left eye became similarly affected. Later, both eyes had iris bombé with secondary glaucoma. On clinical grounds, the condition was diagnosed by several consultants as tuberculous. Agglutination tests for Brucella melitensis and Brucella abortus gave negative results. A presumptive diagnosis of brucellosis was based on the positive results in the cutaneous and opsonocytophagic tests. A carefully regulated course of an oxidized Br. abortus vaccine (Foshay vaccine) led to remarkable clearing of both corneas and great diminution of vascularity. Both eyes were successfully operated on for the secondary glaucoma.

Green concludes that adequate laboratory tests for brucellosis should be made routinely in any case of a chronic inflammatory condition of the cornea, iris, ciliary body or uveal tract. Such tests should be made early in the course of the ocular disease. If other causes can be excluded, prompt and energetic treatment with a brucella vaccine may prove to be the means of checking the progress of the disease, and thus prevent blindness.

W. ZENTMAYER.

OCULAR ROSACEA. G. WISE, Am. J. Ophth. **26:** 591 (June) 1943.

The present study of rosacea was undertaken primarily to evaluate the various etiologic possibilities, in particular the theory that rosacea is due to riboflavin deficiency. The following conclusions are reached.

"Ocular rosacea occurs following facial rosacea and both are manifestations of the same disease.

"At present the fundamental cause of rosacea is unknown.

"Rosacea is not a manifestation of riboflavin deficiency.

"Previously considered causes of rosacea, such as gastrointestinal disturbances, focal infection, endocrine and other disorders, are not fundamental etiologically, but in some cases may be transient aggravating factors.

"Rosacea probably does not occur in the Negro race.

"Lowered gastric acidity is neither specific for rosacea nor nearly so frequent an accompaniment of it as has previously been thought. Its presence is of no special significance.

"Hyaluronic [acid] ester is not decreased in the cornea of the rat that has become vascularized due to riboflavin deficiency.

"The importance of secondary infection in cases of ocular rosacea has been neglected in the past.

"Except in the unusual and rare cases of severe ocular rosacea without secondary infection, most of the distressing symptoms and sequelae of ocular rosacea are due to secondary infection with staphylococci.

"The secondary infection in ocular rosacea can be controlled in almost all cases with 5-percent

sulfathiazole or sulfadiazine ointment, used locally several times daily.

"Rosacea probably is due to some factor causing vasodilatation in the facial area."

W. ZENTMAYER.

Hygiene, Sociology, Education and History

THE SCOPE OF PREVENTION IN OPHTHALMOLOGY. IDA MANN, Brit. M. J. **2**: 482 (Oct. 16) 1943.

The author, director of the Nuffield laboratory of ophthalmology, Oxford, England, after commenting on the recent publication by Marshall and Seiler (*Brit. J. Ophth.* **26**: 337; 385; 434, 1942), states that though there were at the time of her report 74,000 blind persons in England and Wales, whose maintenance costs the state 4,500,000 pounds annually, nothing has been spent in planning the prevention of blindness. A possible reduction of ocular disease, Dr. Mann believes, could occur mainly as a result of advances in three directions: improvement of the ophthalmic services of the country, education of the public on ophthalmic matters and further research on etiologic factors and therapeutics. The problem of the ophthalmic services of the country is linked with the problems of regional planning and medical education. As for the education of the public, the author suggests that education is needed at three levels. 1. Some biologic and physiologic instruction in schools should be obligatory; it should include an understanding of the mechanism of sight and the nature of binocular vision and of errors of refraction. 2. In adult life authoritative information should be available on such subjects as the care of the eyes and the nature of presbyopia. 3. Most especially, however, instruction is needed on protection of the eye in industry, since most minor injuries are due to the prevalent attitude toward safety-first measures and to ignorance of the possible effects of such injuries. The author believes that research requires greater collaboration between experts in the various branches of science. As advances in ophthalmology of recent years owe practically everything to basic discoveries in physics and chemistry—pharmacology and physiology also cooperating, laboratories would be desirable where physicists, physiologists, biochemists and pathologists, among others, could unite with ophthalmologists for the solving of given problems.

In conclusion, Dr. Mann states that the problems of cataract and glaucoma will require the help of biochemistry for their solution and that uveitis must invoke experimentation in pathology, bacteriology and immunology. Venereal disease is yielding to chemotherapy, and myopia and the abiotrophies probably require genetic research for their understanding. The question of injury includes experiments in the design of protective goggles and work on the best psychologic approach to insure their use.

ARNOLD KNAPP.

Injuries

TRANSIENT SLIT-LAMP APPEARANCE DUE TO CONCUSSION OF SMALL PARTICLES. D. D. S. STEWART and J. P. F. LLOYD, Brit. J. Ophth. **27**: 483 (Nov.) 1943.

A soldier received the "back fire" from the breech of a service rifle. This is described as a part of the exploding gases which escape backward, with which are conveyed very small particles of foreign matter, mainly fragments of incompletely burned charge. Biomicroscopic examination a little less than twenty-four hours from the time of the injury disclosed multiple minute foreign bodies, of various sizes, superficially embedded in the cornea, and many scattered areas of endothelial involvement. At the level of Descemet's membrane and the endothelium were minute gray plaques, disposed somewhat in the manner of the leaves of a formal laurel wreath, the central area being clear. The plaques gave the appearance of a grayish white substance (edema [?]) distributed around the endothelial cells. With a few exceptions at the periphery, these "wreaths" were circular and had an average diameter of about 2 mm., a superficial foreign body being seen to correspond to the center of each wreath. The phenomenon was still present thirty hours after the injury, but no trace could be found fifteen hours later. Vision was unaffected. It is suggested that the gray flecks were optical effects from local variations of the index of refraction.

The article is illustrated.

W. ZENTMAYER.

Lens

COMPARISON OF THE KERATOME-SCISSORS AND GRAEFE-KNIFE INCISIONS FOR CATARACT EXTRACTION. C. S. O'BRIEN, Am. J. Ophth. **26**: 508 (May) 1943.

O'Brien summarizes his article and draws the following conclusions:

"1. The keratome-scissors incision for cataract extraction is simpler and safer than the Graefe-knife incision.

"2. Astigmatism is less after the keratome-scissors incision. In 110 consecutive extractions through keratome-scissor incisions, the astigmatism averaged 1.64 diopters, whereas, with a like number of Graefe-knife incisions, the astigmatism averaged 2.42 diopters.

"3. There was little difference in acuity of vision aside from the fact that a greater percentage of those with very high acuity were operated upon with the keratome-scissors technique."

W. ZENTMAYER.

LANCASTER'S TECHNIQUE OF CATARACT EXTRACTION. K. L. ROPER, Am. J. Ophth. **26:** 540 (May) 1943.

Roper describes and illustrates the instruments and technic employed by Lancaster in the performance of the operation for cataract extraction and gives the following summary and conclusions:

"Dr. Walter B. Lancaster's technique of cataract extraction is described in detail. The importance of careful preliminary treatment and good anesthesia is stressed. Successive steps of his operation are described, the most important being his method of placing corneoscleral sutures before the section is made.

"Results in a series of 27 cases are reported wherein the author followed Dr. Lancaster's technique exclusively.

"The high percentage of intracapsular extractions obtained, the low incidence of complications during and following surgery, and the low amount of astigmatism which resulted all seem to prove the merit of Dr. Lancaster's technique."

The article is illustrated. W. ZENTMAYER.

Methods of Examination

SOME CLINICAL APPLICATIONS OF FLUORESCENCE IN RELATION TO MELANOTIC PIGMENT. T. L. TERRY, Am. J. Ophth. **26:** 536 (May) 1943.

Terry gives the following summary of the clinical application of fluorescence to melanotic pigment:

"Why hidden or obscured freckles in the skin or conjunctiva are so dramatically demonstrated under filtrated ultraviolet light in the true, rich brown color of melanin is not obvious.

"Relatively unpigmented tissues containing potentiality of pigmentation, such as unpigmented melanomata and unpigmented nevi, almost invariably appear to be heavily loaded with rich brown pigment under filtered ultraviolet illumination from the mercury-vapor lamp, a finding of perhaps real clinical value.

"Under conditions proper for fluorescence, unpigmented nevi usually appear too large to be removed completely, in many instances discouraging attempts at excision."

W. ZENTMAYER.

OBJECTIVES OF ORTHOPTIC EXAMINATION AND TREATMENT. A. LINKSZ, Am. J. Ophth. **26:** 552 (May) 1943.

This article deals with the objectives of orthoptic examination and does not lend itself to abstraction. W. ZENTMAYER.

Ocular Muscles

ANISOCYCLOPLEGIA. S. J. BEACH, Am. J. Ophth. **26:** 522 (May) 1943.

The term anisocycloplegia is coined to describe a caprice of cycloplegia such that one eye of a person is affected by the drug to a considerably greater degree than the fellow eye. Different methods of administration of the drug do not appreciably or consistently alter the situation. The phenomenon appears to be a property of the individual eye and to be independent of the method of administration. While it may be deceptive to any examiner taught to rely entirely on cycloplegics, it is a menace chiefly to ophthalmologists who are accustomed to base the prescription either on the unverified cycloplegic acceptance or the retinoscopic findings. The condition is revealed by the tests for depth of cycloplegia and by comparison with results of noncycloplegic procedures. W. ZENTMAYER.

Retina and Optic Nerve

DIATHERMY COAGULATION IN THE TREATMENT OF ANGIOMATOSIS RETINAE AND OF JUVENILE COATS'S DISEASE: REPORT OF TWO CASES. J. S. GUYTON and F. H. MCGOVERN, Am. J. Ophth. **26:** 675 (July) 1943.

The authors report a case of bilateral angiomatosis retinae in which diathermy coagulation gave gratifying results and a case of juvenile Coats's disease in which diathermy treatment apparently checked the progress of the disease.

In the first case, of early angiomatosis retinae of the right eye and advanced angiomatosis retinae of the left eye, the angiomatous masses were obliterated by diathermy coagulation. The sites of the angiomatous masses became scars, and the dilated retinal vessels were reduced in size. Vision was completely preserved in the right eye, and the ophthalmoscopic appearance of the left eye improved, although vision was not regained.

In the second case, of early juvenile Coats's disease of the right eye and complete blindness of the left eye, due to massive exudative retinitis, the left eye was enucleated because of early phthisis. Histologic examination of this eye showed a few areas of capillary proliferation in the retinal lesions, somewhat suggestive of angiomatosis retinae. The primary peripheral lesion in the retina of the right eye, which had steadily progressed in size for eleven months, was obliterated with diathermy punctures. The site of the peripheral lesion became a scar; edema of the disk and a subretinal exudate below the disk disappeared, and vision was completely preserved. W. ZENTMAYER.

Vision

TEST CHARTS REPRESENTING A VARIETY OF VISUAL TASKS. M. LUCKIESH, Am. J. Ophth. **27:** 270 (March) 1944.

Luckiesh points out that contrast sensitivity, or the ability to see differences in brightness, is an important factor in seeing and that visual acuity, as measured by the common black on white chart, has gross limitations when applied to everyday seeing.

W. S. REESE.

DEFECTIVE NIGHT VISION AMONG SOLDIERS: DARK ADAPTATION RESULTS AND THEIR USE IN DIAGNOSIS. I. C. MICHAELSON, Brit. J. Ophth. **28:** 140 (March) 1944.

The purpose of the investigation was the determination of: (*a*) the reliability of the Koch dark adaptometer, (*b*) the normal values for minimum form and light senses on the instrument and (*c*) the minimum form and light senses in subjects complaining of defective night vision, and the arrival at a differential diagnosis between psychogenic and organic defects in night vision.

The following conclusions were reached:

"The normal minimal light and form senses vary, but together afford sufficient if not a complete measure of the individual ability to see in the dark.

"Cases of defective night vision have a poor minimum form sense. Many individuals without defective night vision have a poor minimum form sense.

"Measurement of minimum light sense after three minutes' dark adaptation in cases of defective night vision does not appear to have much diagnostic significance.

"Measurement of minimum form sense after three minutes' dark adaptation in cases of defecvision does appear to be diagnostically useful. There are indications that in such cases a poor minimum light sense is associated with organic disturbance, and a good minimum light sense with functional disturbance, as the cause of the defective night vision. Although the groups examined are not large, the data are suggestive and sufficient to indicate further investigations and tentative measures in treatment and disposal.

"Dark adaptometers which measure the minimum form sense and not the minimum light sense have a limited usefulness for two reasons. First, there is a great variation in the minimum form sense among the non-complainers of defective night vision, and secondly, such instruments cannot help in the discrimination between physiogenic and psychogenic defective night vision in the manner detailed above. It cannot be overemphasized that this differential diagnosis is one of the main pre-occupations of oculists investigating complaints of defective night vision among large groups of people."

W. ZENTMAYER.

Therapeutics

TREATMENT OF OCULAR INFECTIONS WITH PENICILLIN. G. T. WILLOUGHBY CASHELL, Brit. M. J. **1:**420 (March 25) 1944.

The author finds that penicillin holds an important place in the treatment of ocular infections, such as acute conjunctivitis, blepharitis, corneal ulcer, perforating corneal injury and dacryocystitis. The remedy is found effective in cases of infection with Staphylococcus aureus and the hemolytic streptococcus, pneumococcus and gonococcus. The optimal strength is 500 oxford units per cubic centimeters, used in the form of drops or ointment. The substance is applied frequently at first, and then the frequency is reduced after the acute stage. Irrigation of the anterior chamber can be carried out with a solution of the drug in certain cases in which the infection has taken place through a perforating wound. It should be remembered that the penicillin loses its potency after fourteen days, and the solution should be stored in a refrigerator. The results in cases of the following conditions are briefly described: blepharitis, 20 cases, acute conjunctivitis, 10 cases; corneal ulcer, 10 cases; perforating injury, 14 cases, and dacryocystitis, 3 cases. A report of cultures and suggestions for dosage are made.

ARNOLD KNAPP.

Toxic Amblyopia

THE OCULAR PATHOLOGY OF METHYL ALCOHOL POISONING. W. H. FINK, Am. J. Ophth. **26:** 694 (July); 802 (Aug.) 1943.

A comprehensive survey of the literature, a series of animal experiments and a report of 3 cases of fatal outcome are used as a basis for formulation of a more definite concept of the process and the nature of the pathologic changes in the eye associated with methyl alcohol poisoning.

As a result of this study certain facts were evident.

There exists an uncertainty concerning the action of methyl alcohol on the eye. The ocular tissues show characteristic pathologic changes.

Choroid.—A study of the microscopic data available indicates the presence of vascular congestion and edema, with little evidence of an inflammatory reaction.

Retina.—The toxic effect first makes itself evident in the ganglion cells. Then the inner nuclear layer degenerates, later the outer nuclear layer and, finally, the layer of rods and cones. It was

observed that if the layer of ganglion cells was greatly changed, other elements of the retina were also considerably affected. The general picture of changes in the retina, in addition to the degenerative process, is that of dropsical saturation.

Optic Nerve.—There is definite evidence that degenerative changes occur in the optic nerve. Signs of edema accompany these degenerative changes to a variable degree.

The various ocular changes are similar, and all the affected tissues become involved simultaneously. Because of its delicate tissue, the reaction is more evident in the retina than in the nerve. Pathologic changes are fundamentally degenerative and occur as the result not only of the action of a toxic substance but of a metabolic disturbance due to the toxin.

The general observations at autopsy indicate pathologic changes of much the same type as those seen in the eye.

Methyl alcohol is broken down into other chemical substances, and one or more of these may be the cause of a toxic reaction greater than that caused by methyl alcohol itself. The pathologic change is the result of the direct action of the toxic substance on the tissues. The toxic substance produces a degenerative change in the tissue, especially the highly differentiated tissue, such as the cells in the retina and, to a lesser degree, the nerve fibers. That this is not an inflammatory change is evident from the absence of an inflammatory reaction. Edema of the nerve tissue and supporting tissue is the result both of irritative reaction of the tissue to the toxic substance and of the degenerative process.

W. H. FINK.

Society Transactions

EDITED BY DR. W. L. BENEDICT

COLLEGE OF PHYSICIANS OF PHILADELPHIA, SECTION ON OPHTHALMOLOGY

WARREN S. REESE, M.D., *Chairman*

GEORGE F. J. KELLY, M.D., *Clerk*

Jan. 20, 1944

Intraocular Pressure and Its Relation to Retinal Extravasation. DR. JOSEPH IGERSHEIMER, Boston.

This paper was published in full in the July issue of the ARCHIVES, page 50.

Marcus Gunn Phenomenon. DR. EDMUND B. SPAETH and DR. JAMES S. SHIPMAN.

Two cases of the Marcus Gunn phenomenon were presented. In the first case the eyeballs were completely immobile, owing to surgically demonstrable fibrosis of all the extraocular muscles. The levator palpebrae superioris muscles, however, were noted at operation to be normal. Elevation of the lids in this case was bilateral and was associated with both opening and closing of the jaws. In the second case the phenomenon was unilateral. The classic picture of elevation of the right lid associated with action of the contralateral pterygoid muscle was present.

The cause and the theories connected with the development of this syndrome were discussed; the cases were illustrated by moving pictures, and the operation for correction of the syndrome was described.

DISCUSSION

DR. F. C. GRANT: The pathways over which the afferent fibers pass to produce this phenomenon are so shrouded in mystery that it is unnecessary to discuss them. I cannot add much to what Dr. Spaeth has said. Dr. Lewy and Dr. Groff, at my suggestion, did some work on this subject which seemed to indicate that the first division of the trigeminal nerve is concerned with the phenomenon to a considerable degree, but these experiments were not nearly as conclusive as we had hoped. I was much interested in having the opinion of an ophthalmologist on the treatment of this condition.

About five years ago my associates and I had a patient who presented the same symptoms as did Dr. Spaeth's second patient, with elevation of one eyelid on contralateral movement of the jaw, a condition suggesting that the innervation of the pterygoid muscle on the same side was always involved, for when that muscle was moved there was a corresponding elevation of the eyelid. In our groping neurologic way, we hypothesized that if the movements of the pterygoid muscle were interfered with, and it was impossible for the patient to move his jaw to the opposite side, the upward movement of the lid might thereby be prevented.

(Slide) When the patient moved his jaw to the right or when the mouth was opened in the midline, the right eyelid was immobile. The full face view shows the Gunn phenomenon, namely, a slight increase in the size of the palpebral fissure on the right side.

(Slide) Acting on the idea that if the movement of the pterygoid muscle on the affected side could be prevented the elevation of the lid on that side might be abolished, we blocked the third division of the fifth nerve on the right side with procaine and found that the patient could not move his jaw to the left, evidence that the motor root was paralyzed and that he had no upward movement of the eyelid. On reenforcement of the procaine with alcohol, 95 per cent of the function of the pterygoid muscle was lost, and he still could move his jaw about ¼ inch (0.6 cm.) to the left. With that movement, or effort, he still had the spasm of the eyelid. We then cut the third division of the right fifth nerve, together with the motor root. We got into serious trouble, for the patient had a postoperative hemorrhage that almost cost him his life. As a result of this complication, he had complete paralysis of the motor fifth nerve, and with that degree of paralysis he could not move his jaw to the left. In consequence, he had none of the previous associated movement. He recovered completely from the paralysis of the third and seventh nerves. The slide shows the result about eight months after operative intervention. There was slight evidence of the oculomotor weakness, but it was impossible for him to move his jaw to the left. Even with forcible movement of the jaw, there was none of the associated movement which had accompanied the contraction of the pterygoid muscle prior to operation.

Frankly, I do not know that I advise operative treatment of such a condition, especially if it may involve the possible hazards consequent to postoperative hemorrhage. Fortunately, this is an uncommon complication.

If there is an ophthalmologic surgical measure to offer such a patient, I think it preferable to the surgical procedure we attempted in this case. Our only excuse for operating on this patient was our

finding in the literature 100 cases of the Marcus Gunn phenomenon, in none of which any attempt had been made to correct the associated movement.

DR. WILLIAM ZENTMAYER: Syndromes showing anomalous associated movements of the muscles of the face and of the eye have been classified by Friedenwald as follows: (1) contraction of the levator palpebrae superioris muscle with movement of the jaw or with swallowing; (2) contraction of the orbicularis muscle in association with movement of the jaw, or contraction of the various facial muscles after facial paralysis, and (3) contraction of the levator palpebrae superioris muscle in association with abduction or adduction of the eye. To these, I should add contraction of the frontalis muscle in association with abduction of the eye.

The committee appointed by the Ophthalmological Society of the Royal Kingdom to report on Gunn's case stated the opinion that the phenomenon was to be explained by innervation of the levator palpebrae superioris muscle both from the nucleus of the third nerve and from the external pterygoid portion of the nucleus of the fifth nerve.

In Harlan's case, reported before this section, rapid winking of the left eye during mastication, which gave the impression of blepharospasm, was an acquired condition, following an attack of typhoid, in a child aged 4 years.

According to Harman and Topolanski (*Wien. med. Bl.,* 1898), elevation of the alae of the nose accompanied normal blinking of the eyes in 20 per cent of persons examined. Harman explained the Gunn phenomenon as representing an atavistic anomaly. In the shark, for example, the fifth and seventh nerves are so closely associated that they are called the "facial complex."

Fuchs has described a syndrome in which the upper lid is raised in attempts at adduction and falls in abduction of the eyeball. The reverse of this may also at times be observed. Usually there is associated ptosis, and there may or may not be paresis of the internal rectus muscle. Fuchs assumed that the excessive nerve energy which is supplied to the paralyzed nerve overflows into the neighboring nuclei.

My own case of contraction of the frontalis muscle associated with abduction of the eyeball occurred in a man aged 20, with hyperopia and esotropia of 12 degrees. His right eye was the fixing eye. There was some limitation of the outward excursion of the left eye. As the object of fixation was carried to the left, the movement of the left eye stopped when the object reached the midline, and the elevation of the left brow began as soon as abduction started and reached its maximum when the eye, by forced action, reached almost the external canthus. There was no accompanying elevation of the lid or widening of the palpebral fissure. There was neither ptosis nor palsy of any of the ocular muscles. Dr. Weisenburg could detect no organic disease of the nervous system. He made a moving picture of the patient and exhibited it before the Philadelphia Neurological Society.

Wilbrand and Sänger (Die Neurologie des Auges, Weisbaden, J. F. Bergmann, 1900, vol. 1, pt. 1, p. 57) reported a case very similar to my own.

DR. FRANCIS HEED ADLER: In the present state of knowledge it is probably fruitless to suggest another explanation of this interesting condition. It is curious, however, that no one has called attention to the possibility of a cortical or subcortical site of the lesion. It is well known that in the vast majority of cases this phenomenon is associated with congenital ptosis. None of the ocular muscles are represented individually in the frontal cortex except for those of the lid. The levator palpebrae muscle is represented in the foot of the second frontal convolution adjacent to the representation of the muscles which move the jaws.

Therefore, a lesion or absence of development of the cells in this area might easily account for this phenomenon. At present, however, there is no evidence on which to base such a hypothesis.

DR. JAMES S. SHIPMAN: I saw the first patient whom Dr. Spaeth presented, and I asked Dr. Spaeth for a consultation. He at once made a diagnosis and suggested the operative procedure which followed. There is a question in my mind whether this procedure will produce permanent results. As Dr. Spaeth pointed out, the Marcus Gunn phenomenon is congenital, and the pseudo Graefe phenomenon is acquired. However, the cause of the pseudo Graefe phenomenon is often the same condition as that produced by the operative procedure followed in this case, i. e., laceration of the fibers to the levator muscle by trauma, with production of ptosis, and, later, regeneration of the nerve fibers to that muscle. Abnormal movements may develop; for example, when the patient is looking down, the eyelid moves up. My associates and I had a case of this type not many months ago.

In Dr. Spaeth's opinion, the basis of the Marcus Gunn phenomenon is a misdirection or an abnormal regeneration of nerve fibers. The question is whether this patient will still present the same appearance three or five years from now that he has at present. Before Dr. Grant gives the ophthalmologists too much credit for the surgical cure of the Marcus Gunn syndrome, a few years should be allowed to elapse.

DR. EDMUND B. SPAETH: I appreciate the discussion on these cases. Dr. Shipman and I will present later a moving picture of the surgical procedure. The longest period that the correction has been, and still is, maintained is a bit over four years. Apparently, the correction is permanent. I see no reason to doubt the permanance of these cures.

Dr. Grant's demonstration of the afferent pathway is convincing. I was interested in Dr. Adler's comment. In my opinion, however, the cause of the Marcus Gunn phenomenon is not cortical stimulation, even though such a relation was indicated by Walsh's patient, who showed elevation of the lid when he became interested in an attractive member of the opposite sex, and by the second patient presented tonight, who had elevation of the upper lid when she became angry.

Precipitous Development of Optic Neuritis and Cataracts Associated with Hypoparathyroidism: Report of a Case. DR. WALTER I. LILLIE.

A case of bilateral optic neuritis and precipitous formation of cataract associated with postoperative hypoparathyroidism is presented. Ophthalmologically the case presented many interesting features.

1. The patient had had mild exophthalmos since the age of 10 years, and this had not changed in character during the entire course of the condition under discussion.

2. Blurring of vision associated with acute bilateral optic neuritis developed precipitously two months after thyroidectomy, but well in advance of any of the clinical signs, such as dermatitis and tetany associated with convulsions. 3. At the time of the first examination at Temple University Hospital, the lens in each eye showed only a few small, discrete opacities in the cortex anterior to the posterior capsule. Opacifications were of so minor a degree that examination of the fundus was not interfered with in either eye. Edema of the disk was visible with the ophthalmoscope. Ocular examination at this time revealed a classic optic neuritis syndrome.

4. The rapid development of cataracts to maturity and hypermaturity in the course of ten days during the patient's stay in the hospital is of great interest. Unfortunately, it prevented any examination of the fundus to determine the response of the optic neuritis to general treatment.

5. After successful extraction of the cataract in each eye, the fundus and the visual acuity were normal.

DISCUSSION

DR. CHARLES L. BROWN: This patient's general condition was complicated, and of course, was associated with an extensive metabolic disturbance. I am inclined to think that not only severe chronic hypoparathyroidism but diminution in the function of the thyroid was involved. There was reason to believe that a nutritional deficiency also entered into the picture.

The last-mentioned point is not clearly understood, but it is apparent in other cases that have been reported. I am thinking particularly of a case which Dr. Norman Learner and I reported (*J. Clin. Endocrinol.* **2**: 261 [May] 1943), in which we were able to demonstrate evidence of nutritional deficiency, especially in vitamin B. In this case, we also had evidence that vitamin D deficiency might play a part. Our patient had cutaneous manifestations, which became evident during the part of the year that this patient was not exposed to the usual amount of sunlight. It is interesting that many of the ectodermal changes that have occurred in connection with postoperative thyroid and parathyroid conditions seem to have been particularly prevalent in patients who were operated on between January and May. The hypoparathyroid state suggests disorders associated with calcium and phosphorus metabolism. How much this widespread metabolic disorder has to do with the formation of cataract and with the occurrence of other changes in ectodermal tissue one can only speculate.

It is not rare for cataract to occur as a manifestation, or feature, of chronic tetany. It is apparent from reports in the literature that cataract was recognized as being frequently associated with the nutritional tetany of young adults. Authors who described such cataracts called attention to the characteristic subcapsular distribution of these opacities. There has been indication that cataracts develop rather rapidly. In a case reported by Emerson, Walsh and Howard (*Ann. Int. Med.* **14**: 1256 [Jan.] 1941) cataract was said to have developed bilaterally, with complete blindness within four and one-half months. An interesting, and perhaps significant, point in Dr. Lillie's case is the rapid appearance of the cataract—within ten days, while the patient was under his observation. It is interesting that dihydrotachysterol with calcium was an effective therapeutic agent in restoration of the calcium phosphorus metabolism to normal. It would have been interesting to see whether this substance would have impeded the progress of formation of these cataracts if they had not been formed so rapidly.

I have never understood the exact nature of the increased intracranial pressure, together with the excessive formation of spinal fluid, in this case.

Foster Kennedy Syndrome with Fusiform Aneurysms of Both Internal Carotid Arteries. DR. I. S. TASSMAN.

This article was published in full in the August 1944 issue of the ARCHIVES, page 125.

DISCUSSION

DR. BERNARD J. ALPERS: It would have been instructive if Dr. Tassman had stated the difficulties experienced by a group of representative oculists in determining whether a Foster Kennedy syndrome was actually present in this case. There was considerable difference of opinion concerning the presence of optic neuritis in the

one eye and the existence of edema. That, I think, is an important point.

The feature of the greatest interest in this case is the so-called Foster Kennedy syndrome. Two problems always develop in a consideration of the possible presence of this syndrome. The first is that some one sooner or later raises the question of nomenclature and states that the condition is not the Kennedy syndrome at all.

The second point is that the thinking about this syndrome has become largely oriented toward a diagnosis of tumor. If one could find some other way of describing the pathologic picture, such as alternating edema and atrophy, ideas with regard to the causal factors might not be so fixed. There is no question that a tumor in the suprasellar region is frequently present with this syndrome, but it is not so often recognized that the condition may be associated with aneurysm and arteriosclerosis of the vessels of the circle of Willis. My associates and I recently had a case of a typical Foster Kennedy syndrome, with edema in one eye and atrophy in the other. The patient had an injury to the head and later headache and loss of visual acuity developed first in one eye and later in the other. The diagnosis was that of tumor. He had a central scotoma in one eye and a field defect in the other. A pneumoencephalogram revealed nothing significant. Operation disclosed arachnoiditis with firm adhesions covering the optic chiasm and both optic nerves. Because there seemed to be bulging over the third ventricle, this area was explored, but nothing was seen in it. It can be stated without hesitation that the syndrome in this case was due to arachnoiditis. It is well to recognize that as more cases of this type of syndrome are encountered, more causes will be evident.

DR. W. I. LILLIE: (Four lantern slides, illustrating various vascular anomalies of the anterior portion of the circle of Willis, were shown.)

These vascular anomalies push the optic nerves upward and forward against the bony roof of the optic canals. This continued pressure produces the typical prechiasmal syndrome described by Dr. Tassman. The operative procedure for relief of pressure is restricted to removal of the bony roof of the optic canal, as the vascular anomaly usually prohibits any surgical intervention.

DR. I. S. TASSMAN: With regard to the differential diagnosis of papilledema and optic neuritis, to which Dr. Alpers referred, the diagnosis of optic neuritis in the right eye was made in her home town. I never believed that the condition in the right eye was anything other than papilledema, particularly in view of the presence of good central vision in that eye. If it had been optic neuritis, central vision would have been much less than it was found to be—practically normal.

Further, there was almost complete absence of any signs of inflammation about the nerve head or the vessels.

News and Notes

GENERAL NEWS

Annual Postgraduate Course, University of Virginia Hospital.—The eleventh annual postgraduate course will be held at the University of Virginia Hospital, in Charlottesville, Va., on Dec. 5, 6, 7 and 8, 1944. The ophthalmologic program will be given on December 7 and 8, under the direction of Dr. Edward W. Burton, who is in charge of the section of ophthalmology. The invited faculty will include Dr. James W. White, of New York, who will speak on muscular anomalies; Dr. Paul A. Chandler, of Boston, who will give lectures on disorders of the lacrimal passages, glaucoma and cataract; Dr. Wilfred E. Fry, of Philadelphia, who will lecture on diseases of the optic nerve, and Dr. Wendell L. Hughes, of Hempstead, N. Y., who will speak on repair of lacerations of the lid and reconstruction of the socket and of the lower lid.

CORRECTION

In the article by Dr. Richard Waldapfel entitled "Infection of Lymphoid Tissue of the Pharynx and of the Conjunctiva," in the April issue (ARCH. OPHTH. **31**: 331-333, 1944), the *D* and the *B* in the legend under the picture on page 332 are reversed; in other words, in the third line of the legend *D* (case 1) should read *B*, and in the eighth line *B* (case 2) should read *D*.

Book Reviews

Cataract and Anomalies of the Lens. Growth, Structure, Composition, Metabolism, Disorders and Treatment of the Crystalline Lens. By John G. Bellows, M.D., Ph.D. Price, $12. Pp. 624, with 208 illustrations and 4 colored plates. St. Louis: C. V. Mosby Company, 1944.

This book consists of 624 pages, of which about 291 pages comprise the text. There are excellent illustrations, a good index of subjects and a separate index of authors. At the end of each of the ten chapters there is a complete list of references, with titles. The foreword is by the late Dr. Sanford R. Gifford, to whose memory the book is dedicated.

Chapter I, consisting of about 28 pages of text, is ambiguously entitled "The History of the Crystalline Lens." It describes the evolution of knowledge of the lens from 2250 B.C. to modern times. Accommodation and the optical properties of the lens are not dealt with at length anywhere in the book, but in this chapter more than a page is given to proof that accommodation depends on change in shape of the lens.

Chapter II deals with the embryonic development of the lens in lower animals and in man and includes a mathematical consideration of the growth of the lens. It also deals with induction and regeneration of the lens, including formation of secondary cataracts and Elschnig bodies.

Chapter III deals with the structure of the lens in lower animals and in man. Neither the embryonic nor the adult nucleus is described as such, although they are referred to in later chapters.

Chapter IV deals with the chemical composition of normal and of cataractous lenses and with the immunologic properties of the lens. Phacoanaphylactic endophthalmitis is discussed somewhat at length, but its histologic characteristics are not described. It is astonishing that since the discovery of this condition, twenty-two years ago, nothing of definite clinical value has emerged from the enormous amount of investigative work referred to in this and in the next chapter.

Chapter V deals with the metabolism of the lens and with capsular permeability. These are subjects of the author's personal investigation, but he does not emphasize his contributions.

Chapter VI is entitled "Developmental Defects of the Crystalline Lens." It includes consideration not only of malformations of the lens, congenital aphakia and ectopia lentis, which are certainly developmental defects, but also of such conditions as coralliform, zonular and tetanic cataracts, which are chiefly dependent on metabolic disturbances.

Chapter VII deals with cataracts due to radiant energy, electricity, deficiency of vital constituents and toxins. The author concludes that it is unlikely that exposure to ultraviolet light is significant in the causation of senile cataract but seems to accept Vogt's contention that glassblowers' cataract (heat cataract) is due to specific action of infra-red rays.

Chapter VIII deals with cataracta complicata, cataracts due to trauma and displacements of the lens. Two pages are given to a discussion of siderosis of the lens. The author does not mention the fact that the deposits in the capsular epithelium tend to occur in the form of two rings, one behind the pupillary border and the other at the place where the iris leaves contact with the lens. He mentions von Hippel's explanation of siderosis but does not give it fully, and states that the best explanation is that of Itoi. To the reviewer, von Hippel's hypothesis is the more satisfying for it explains why the iron granules are deposited chiefly in certain cells, notably in the epithelial cells of the capsule, in the cells of the pigment epithelium and the unpigmented layer of the pars ciliaris retinae and in the cells of the dilator iridis.

Chapter IX deals with cataract due to endocrine dysfunction, including diabetic cataract, cataracta parathyreopriva and the cataracts associated with dystrophia myotonica, hypothyroidism, mongolism and dermatologic disturbances.

Chapter X is concerned with senile cataract. Here the pathogenesis of this form of cataract is separately discussed. Considerable repetition could have been avoided if the few additional facts mentioned in this connection had been incorporated in chapters VIII and IX. The pathologic histology of senile cataract is inadequately described and is not illustrated at all. The author does not discuss, or even mention, the anterior capsular cataract often associated with senile and other types of cataract and hence does not point out the remarkable fact that the capsular epithelium can produce tissue closely resembling, if not identical with, mesoblastic connective tissue. He, also, does not point out that a morgagnian cataract can cause glaucoma or, by its spontaneous rupture, produce characteristic intraocular inflammation, with disastrous consequences. The title of a subsection in this chapter is "Is the Control of Cataract Possible?" The author does not definitely answer this question, but from the facts presented the reviewer concludes that no nonoperative treatment that will prevent senile cataract or delay its progress has yet been proposed. The author states, without dissenting, that Schoen and Jackson "emphasize the fact

that strain, particularly during accommodation, alters the lens nutrition in some manner, producing a cataract." The reviewer questions the "fact" and suggests that the "strain" may even tend to prevent cataract by improving the nutrition of the lens. About 10 pages are given to the operative treatment of cataract and another 10 pages to postoperative complications. These two presentations are excellent so far as they go but are too incomplete to be of great value.

The format of the book is excellent. The text is clear and well arranged. It is so well worded that it is surprising to find "intraocular tension" invariably used instead of the correct term "intraocular pressure."

It is to be noted that the criticisms made in this review are comparatively unimportant and relate chiefly to omissions. With respect to the value of the book as a whole, the reviewer concurs in the opinion expressed by Dr. Gifford in the foreword: "Certainly this material cannot be found elsewhere in a single volume or in many volumes. . . . There seems to be no doubt he has produced an exceedingly interesting and important work, one which will take its place as the authority on the crystalline lens."

F. H. VERHOEFF.

Intracranial Arterial Aneurysms. By Walter E. Dandy. Price, $2.50. Pp. 147, with 55 illustrations and 6 charts. Ithaca, N. Y.: Comstock Publishing Co., Inc., 1944.

As a measure of the progress of neurosurgery in the last thirty years, it may be recalled that all knowledge on the localization and surgical treatment of tumors of the brain in 1914 could easily have been printed in a volume the size of this one, which does not discuss even all tumors of blood vessels (angiomas are not considered) but considers only intracranial aneurysms.

Ophthalmologists have become familiar with the ocular symptoms of intracranial aneurysms through the paper by Walsh and King (Walsh, F. B., and King, A. B.: Ocular Signs of Intracranial Saccular Aneurysms: Experimental Work on Collateral Circulation Through the Ophthalmic Artery, ARCH. OPHTH. **27:** 1 [Jan.] 1942). The material for that paper was to a great extent derived from Dandy's series, and there is therefore a certain similarity between the description by Walsh and King and that in the present book. One finds again those curious denervation phenomena referable to degeneration of the third nerve and the anomalous movements of the eyeball and upper lid due to a misdirection of the regenerated fibers. At a certain stage of regeneration of a paralyzed third nerve, an Argyll Robertson pupil has been observed. When the aneurysm is large enough, papilledema may result; but in some patients retinal hemorrhages have been observed without papilledema—large, round, subhyaloid hemorrhages, thought to be pathognomonic of subarachnoid bleeding and of an aneurysm on the same side. An anterior aneurysm is of course apt to bring pressure on the visual pathway.

The following symptoms are most frequently associated with aneurysm in various locations:

1. Internal carotid artery in the carotid canal: pain, severe and sudden, in the region of the eye and the frontal area, often associated with paralysis of the third nerve; involvement of the trigeminal nerve; paralyses of the fourth and sixth nerves; direct pressure on an optic tract or an optic nerve, and occasionally on the chiasm, and exophthalmos, if the aneurysm is large enough to erode the walls of the sphenoid fissure and push the orbital content forward.

2. Intracranial portion of the internal carotid artery.

(*a*) Diffuse dilatation of the trunk of the artery: homolateral primary optic nerve atrophy.

(*b*) Small sacculated aneurysm proximal to the origin of the branches: paralysis of the third nerve.

(*c*) Aneurysm of the internal carotid artery at or near its branches: paralysis of the third nerve; retinal hemorrhages without papilledema.

3. Anterior cerebral artery and anterior communicating artery: pressure on the optic nerves and optic chiasm; paralyses of the extraocular muscles in some cases.

4. Middle cerebral artery: subhyaloid hemorrhages of the retina without papilledema.

5. Posterior cerebral artery: paralyses of the third, fourth and sixth nerves. If the aneurysm develops in the brain substance, it is indistinguishable from a neoplasm in the same region, and homonymous hemianopsia or visual aphasia may be present.

It is evident that a paralysis of the third nerve is one of the most frequent symptoms (30 per cent of all cases in this series) and that it is particularly suggestive of an aneurysm of the internal carotid artery.

Ophthalmologists may be interested to learn that many aneurysms have a congenital origin and are due to the incomplete involution of temporary arteries. The primitive ophthalmic artery is one of the vessels which are responsible for such aneurysms.

An interesting chapter deals with the embryology and anatomy of the circle of Willis, and another is devoted to the surgical treatment. It is encouraging to know that in the last twenty years 64 aneurysms were treated surgically. In the last six and one-quarter years, 36 cases of aneurysm were observed; in 30 of these operation was performed, with cure in 21 cases and death in only 9 cases.

The book is evidently designed to be read by neurosurgeons, and the author has therefore dealt in detail with the operative procedures; but there is much which will interest the ophthalmologist. The print and illustrations are clear.

EDWARD HARTMANN.

Directory of Ophthalmologic Societies *

INTERNATIONAL

International Association for Prevention of Blindness

President: Dr. P. Bailliart, 66 Boulevard Saint-Michel, Paris, 6e, France.
Secretary-General: Prof. M. Van Duyse, Université de Gand, Gand, Prov. Ostflandern, Belgium.
All correspondence should be addressed to the Secretariat, 66 Boulevard Saint-Michel, Paris, 6e, France.

International Ophthalmologic Congress

President: Prof. Nordenson, Serafimerlasarettet, Stockholm, Sweden.
Secretary: Dr. Ehlers, Jerbanenegade 41, Copenhagen, Denmark.

International Organization Against Trachoma

President: Dr. A. F. MacCallan, 17 Horseferry Rd., London, England.

Pan-American Congress of Ophthalmology

President: Dr. Harry S. Gradle, 58 E. Washington St., Chicago.
Executive Secretaries: Dr. Conrad Berens, 35 E. 70th St., New York. Dr. M. E. Alvaro, 1511 Rua Consolacão, São Paulo, Brazil.

FOREIGN

All-India Ophthalmological Society

President: Dr. B. K. Narayan Rao, Minto Ophthalmic Hospital, Bangalore.
Secretary: Dr. G. Zachariah, Flitcham, Marshall's Rd., Madras.

British Medical Association, Section on Ophthalmology

President: Dr. W. Clark Souter, 9 Albyn Pl., Aberdeen, Scotland.
Secretary: Dr. Frederick Ridley, 12 Wimpole St., London, W. 1.

Chengtu Ophthalmological Society

President: Dr. Eugene Chan.
Secretary: Dr. K. S. Sun.
Place: Eye, Ear, Nose and Throat Hospital, Chengtu, China.

Chinese Ophthalmology Society

President: Dr. C. H. Chou, 363 Avenue Haig, Shanghai.
Secretary: Dr. F. S. Tsang, 221 Foochow Rd., Shanghai.

Chinese Ophthalmological Society of Peiping

President: Dr. H. T. Pi, Peiping Union Medical College, Peiping.
Secretary: Dr. C. K. Lin, 180 Hsi-Lo-yen Chienmeng, Peiping.
Place: Peiping Union Medical College, Peiping. Time: Last Friday of each month.

German Ophthalmological Society

President: Prof. W. Lohlein, Berlin.
Secretary: Prof. E. Engelking, Heidelberg.

Hungarian Ophthalmological Society

President: Prof. I. Imre, Budapest.
Assistant Secretary: Dr. Stephen de Grósz, University Eye Hospital, Máriautca 39, Budapest.
All correspondence should be addressed to the Assistant Secretary.

Midland Ophthalmological Society

President: Dr. W. Niccol, 4 College Green, Gloucester, England.
Secretary: Mr. T. Harrison Butler, 61 Newhall St., Birmingham 3, England.
Place: Birmingham and Midland Eye Hospital.

North of England Ophthalmological Society

President: Mr. John Foster, 45 Park Sq., Leeds.
Secretary: Mr. William M. Muirhead, 70 Upper Hanover St., Sheffield.
Place: Manchester, Bradford, Leeds, Newcastle-upon-Tyne, Liverpool and Sheffield, in rotation. Time: October to April.

Ophthalmological Society of Australia

President: Dr. A. James Flynn, 135 Macquarie St., Sydney.
Secretary: Dr. D. Williams, 193 Macquarie St., Sydney.

Ophthalmological Society of Egypt

President: Prof. Dr. Mohammed Mahfouz Bey, Government Hospital, Alexandria.
Secretary: Dr. Mohammed Khalil, 4 Baehler St., Cairo.
All correspondence should be addressed to the secretary, Dr. Mohammed Khalil.

Ophthalmological Society of the United Kingdom

President: Mr. Charles B. Goulden, O.B.E., M.D., M.Ch., 89 Harley St., London.
Secretary: Mr. Frank W. Law, M.A., M.D., F.R.C.S., 30 Devonshire Pl., London W. 1.

Ophthalmology Society of Bombay

President: Dr. D. D. Sathaye, 127 Girgaum Rd., Bombay 4, India.
Secretary: Dr. H. D. Dastur, Dadar, Bombay 14, India.
Place: H. B. A. Free Ophthalmic Hospital, Parel, Bombay 12. Time: First Friday of every month.

Oxford Ophthalmological Congress

Master: Mr. P. G. Doyne, 60 Queen Anne St., London, W. 1, England.
Secretary-Treasurer: Dr. F. A. Anderson, 12 St. John's Hill, Shrewsbury, England.
Place: Oxford, England. Time: July 8-9, 1943.

Palestine Ophthalmological Society

President: Dr. Arieh Feigenbaum, Abyssinian St. 15, Jerusalem.
Secretary: Dr. E. Sinai, Tel Aviv.

Polish Ophthalmological Society

President: Dr. W. Kapuściński, 2 Waly Batorego, Poznań.
Secretary: Dr. J. Sobański, Lindley'a 4, Warsaw.
Place: Lindley'a 4, Warsaw.

Royal Society of Medicine, Section of Ophthalmology

President: Col. F. A. Juler, 96 Harley St., London, W. 1, England.
Secretary: Dr. Harold Ridley, 60 Queen Anne St., London, W. 1, England.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and keep it up to date.

São Paulo Society of Ophthalmology

President: Prof. Moacyr E. Alvaro, Consolação 1151, São Paulo, Brazil.

Secretary: Dr. Silvio de Almeida Toledo, Enfermaria Santa Luzia, Santa Casa de Misericordia, Cesario Motta, St. 112, São Paulo, Brazil.

Scottish Ophthalmological Club

President: Dr. S. Spence Meighan, 13 Woodside Pl., Glasgow, C. 3.

Secretary: Dr. Alexander Garrow, 15 Woodside Pl., Glasgow, C. 3.

Place: Edinburgh and Glasgow, in rotation.

Sociedad Argentina de Oftalmologia

Chairman: Dr. Jorge Malbrán, Buenos Aires.

Secretary: Dr. Benito Just Tiscornia, Santa Fe 1171, Buenos Aires.

Sociedad Oftalmologia del Litoral, Rosario (Argentina)

President: Prof. Dr. Carlos Weskamp, Laprida 1159, Rosario.

Secretary: Dr. Juan M. Vila Ortiz, Córdoba 1433, Rosario.

Place: Rosario. Time: Last Saturday of every month, April to November, inclusive. All correspondence should be addressed to the President.

Sociedade de Oftalmologia de Minas Gerais

President: Prof. Hilton Rocha, Rua Rio de Janeiro 2251, Bello Horizonte, Minas Geraes, Brazil.

Secretary: Dr. Ennio Coscarelli, Rua Aimorés 1697, Bello Horizonte, Minas Geraes, Brazil.

Sociedade de Oftalmologia e Otorrinolaringologia de Rio Grande do Sul

President: Dr. Luiz Assumpção Osorio, Edificio Vera Cruz, Apartamento 134, Porto Alegre, Rio Grande do Sul.

Secretary: Dr. Fernando Voges Alves, Caixa Postal 928, Porto Alegre, Rio Grande do Sul.

Sociedade de Ophthalmologia e Oto-Rhino-Laryngologia da Bahia

President: Dr. Theonilo Amorim, Barra Avenida, Bahia, Brazil.

Secretary: Dr. Adroaldo de Alencar, Brazil.

All correspondence should be addressed to the President.

Società Oftalmologica Italiana

President: Prof. Dott. Giuseppe Ovio, Ophthalmological Clinic, University of Rome, Rome.

Secretary: Prof. Dott. Epimaco Leonardi, Via del Gianicolo, 1, Rome.

Société Française d'Ophtalmologie

Secretary: Dr. René Onfray, 6 Avenue de la Motte Picquet, Paris, 7e.

Society of Swedish Ophthalmologists

President: Prof. K. G. Ploman, Stockholm.

Secretary: Dr. K. O. Granström, Södermalmstorg 4 Ill tr., Stockholm, Sö.

Tel Aviv Ophthalmological Society

President: Dr. D. Arieh-Friedman, 96 Allenby St., Tel Aviv, Palestine.

Secretary: Dr. Sadger Max, 9 Bialik St., Tel Aviv, Palestine.

NATIONAL

American Medical Association, Scientific Assembly, Section on Ophthalmology

Chairman: Dr. Frederick C. Cordes, 384 Post St., San Francisco.

Secretary: Dr. R. J. Masters, 23 E. Ohio St., Indianapolis.

Place: New York. Time: June 11-15, 1945.

American Academy of Ophthalmology and Otolaryngology, Section on Ophthalmology

President: Dr. Lawrence T. Post, Metropolitan Bldg., St. Louis.

President-Elect: Dr. Gordon B. New, Mayo Clinic, Rochester, Minn.

Executive Secretary-Treasurer: Dr. William L. Benedict, 101–1st Ave. Bldg., Rochester, Minn.

American Ophthalmological Society

President: Dr. S. Judd Beach, 704 Congress St., Portland, Maine.

Secretary-Treasurer: Dr. Walter S. Atkinson, 129 Clinton St., Watertown, N. Y.

Association for Research in Ophthalmology, Inc.

Chairman: Dr. Conrad Berens, 35 E. 70th St., New York.

Secretary-Treasurer: Major Brittain F. Payne, School of Aviation Medicine, Randolph Field, Texas.

Assistant Secretary-Treasurer: Dr. Hunter Romaine, 35 E. 70th St., New York.

Canadian Medical Association, Section on Ophthalmology

President: Dr. Alexander E. MacDonald, 170 St. George St., Toronto.

Secretary-Treasurer: Dr. L. J. Sebert, 170 St. George St., Toronto.

Canadian Ophthalmological Society

President: Dr. R. Evatt Mathers, 34½ Morris St., Halifax, N. S.

Secretary-Treasurer: Dr. Kenneth B. Johnston, Suite 1, 1509 Sherbrooke St. W., Montreal.

National Society for the Prevention of Blindness

President: Mr. Mason H. Bigelow, 1790 Broadway, New York.

Secretary: Miss Regina E. Schneider, 1790 Broadway, New York.

Executive Director: Mrs. Eleanor Brown Merrill, 1790 Broadway, New York.

SECTIONAL

Academy of Medicine of Northern New Jersey, Section on Eye, Ear, Nose and Throat

President: Dr. N. Zwaifler, 46 Wilbur Ave., Newark.

Secretary: Dr. William F. Keim Jr., 25 Roseville Ave., Newark.

Place: 91 Lincoln Park South, Newark. Time: 8:45 p. m., second Monday of each month, October to May.

Central Wisconsin Society of Ophthalmology and Otolaryngology

President: Dr. L. J. Friend, 425 E. Grand Ave., Beloit, Wis.

Secretary: Dr. G. L. McCormick, 626 S. Central Ave., Marshfield.

NEW ENGLAND OPHTHALMOLOGICAL SOCIETY

President: Dr. Paul A. Chandler, 5 Bay State Rd., Boston.
Secretary-Treasurer: Dr. Merrill J. King, 264 Beacon St., Boston.
Place: Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston. Time: 8 p. m., third Tuesday of each month from November to April, inclusive.

PACIFIC COAST OTO-OPHTHALMOLOGICAL SOCIETY

President: Dr. D. H. O'Rourke, 1612 Tremont Pl., Denver.
Secretary-Treasurer: Dr. C. Allen Dickey, 450 Sutter St., San Francisco.

PUGET SOUND ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President: Dr. L. L. Bull, 1215–14th Ave., Seattle, Wash.
Secretary-Treasurer: Dr. Barton E. Peden, 301 Stimson Bldg., Seattle 1.
Place: Seattle or Tacoma, Wash. Time: Third Tuesday of each month except June, July and August.

ROCK RIVER VALLEY EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. J. Sheldon Clark, 27 E. Stephenson St., Freeport, Ill.
Secretary-Treasurer: Dr. Harry R. Warner, 321 W. State St., Rockford, Ill.
Place: Rockford, Ill., or Janesville or Beloit, Wis. Time: Third Tuesday of each month from October to April, inclusive.

SAGINAW VALLEY ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. M. H. Pike, Midland, Mich.
Secretary-Treasurer: Dr. H. H. Heuser, 207 Devidson Bldg., Bay City, Mich.
Place: Saginaw or Bay City, Mich. Time: Second Tuesday of each month, except July, August and September.

SIOUX VALLEY EYE AND EAR ACADEMY

President: Dr. J. C. Decker, 515 Francis Bldg., Sioux City, Iowa.
Secretary-Treasurer: Dr. J. E. Dvorak, 408 Davidson Bldg., Sioux City, Iowa.

SOUTHERN MEDICAL ASSOCIATION, SECTION ON EYE, EAR, NOSE AND THROAT

Chairman: Dr. John H. Burleson, 414 Navarro St., San Antonio, Texas.
Secretary: Dr. J. W. Jervey Jr., 101 Church St., Greenville, S. C.

SOUTHWESTERN ACADEMY OF EYE, EAR, NOSE AND THROAT

President: Dr. H. L. Brehmer, 221 W. Central Ave., Albuquerque, N. Mex.
Secretary: Dr. A. E. Cruthirds, 1011 Professional Bldg., Phoenix, Ariz.

SOUTHWESTERN MICHIGAN TRIOLOGICAL SOCIETY

President: Dr. W. M. Dodge, 716 First National Bank Bldg., Battle Creek.
Secretary-Treasurer: Dr. Kenneth Lowe, 25 W. Michigan Ave., Battle Creek.
Time: Last Thursday of September, October, November, March, April and May.

WESTERN PENNSYLVANIA EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. Ray Parker, 218 Franklin St., Johnston, Pa.
Secretary-Treasurer: Dr. J. McClure Tyson, Deposit Nat'l Bank Bldg., DuBois.

STATE

ARKANSAS STATE MEDICAL SOCIETY, EYE, EAR, NOSE AND THROAT SECTION

President: Dr. Raymond C. Cook, 701 Main St., Little Rock.
Secretary: Dr. K. W. Cosgrove, Urquhart Bldg., Little Rock.

COLORADO OPHTHALMOLOGICAL SOCIETY

President: Dr. C. A. Ringle, 912–9th Ave., Greeley.
Secretary: Dr. W. A. Ohmart, 1102 Republic Bldg., Denver.
Place: University Club, Denver. Time: 7:30 p. m., third Saturday of each month, October to May, inclusive.

CONNECTICUT STATE MEDICAL SOCIETY, SECTION ON EYE, EAR, NOSE AND THROAT

President: Dr. F. L. Phillips, 405 Temple St., New Haven.
Secretary-Treasurer: Dr. W. H. Turnley, 1 Atlantic St., Stamford, Conn.

EYE, EAR, NOSE AND THROAT CLUB OF GEORGIA

President: William O. Martin Jr., Doctors Bldg., Atlanta.
Secretary-Treasurer: Dr. C. K. McLaughlin, 526 Walton St., Macon.

INDIANA ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President: Dr. F. McK. Ruby, Union City.
Secretary: Dr. Edwin W. Dyar Jr., 23 E. Ohio St., Indianapolis.
Place: French Lick. Time: First Wednesday in April.

IOWA ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President: Dr. J. K. Von Lackum, 117–3d St. S. E., Cedar Rapids.
Secretary-Treasurer: Dr. B. M. Merkel, 604 Locust St., Des Moines.

KANSAS STATE MEDICAL SOCIETY, SECTION ON OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. W. D. Pittman, Pratt.
Secretary: Dr. Louis R. Haas, 902 N. Broadway, Pittsburg.

LOUISIANA-MISSISSIPPI OPHTHALMOLOGICAL AND OTOLARYNGOLOGICAL SOCIETY

President: Dr. Val H. Fuchs, 200 Carondelet St., New Orleans.
Secretary-Treasurer: Dr. Edley H. Jones, 1301 Washington St., Vicksburg, Miss.

MICHIGAN STATE MEDICAL SOCIETY, SECTION OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

Chairman: Dr. Robert H. Fraser, 25 W. Michigan Ave., Battle Creek.
Secretary: Dr. R. G. Laird, 114 Fulton St., Grand Rapids.

Minnesota Academy of Ophthalmology and Otolaryngology

President: Dr. George E. McGeary, 920 Medical Arts Bldg., Minneapolis.
Secretary: Dr. William A. Kennedy, 372 St. Peter St., St. Paul.
Time: Second Friday of each month from October to May.

Montana Academy of Oto-Ophthalmology

President: Dr. William Morrison, 208 N. Broadway, Billings, Mont.
Secretary: Dr. Fritz D. Hurd, 309 Medical Arts Bldg., Great Falls.

Nebraska Academy of Ophthalmology and Otolaryngology

President: Dr. W. Howard Morrison, 1500 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. John Peterson, 1307 N St., Lincoln.

New Jersey State Medical Society, Section on Ophthalmology, Otology and Rhinolaryngology

Chairman: Dr B. E. Failing, 31 Lincoln Park, Newark.
Secretary: Dr. George Meyer, 410 Haddon Ave., Camden.

New York State Medical Society, Eye, Ear, Nose and Throat Section

Chairman: Dr. Harold J. Joy, 504 State Tower Bldg., Syracuse 2.
Secretary: Dr. Maxwell D. Ryan, 660 Madison Ave., New York 21.

North Carolina Eye, Ear, Nose and Throat Society

President: Dr. Hugh C. Wolfe, 102 N. Elm St., Greensboro.
Secretary: Dr. Vanderbilt F. Couch, 104 W. 4th St., Winston-Salem.

North Dakota Academy of Ophthalmology and Oto-Laryngology

President: Dr. W. L. Diven, City National Bank Bldg., Bismarck.
Secretary-Treasurer: Dr. A. E. Spear, 20 W. Villard, Dickenson.

Oregon Academy of Ophthalmology and Oto-Laryngology

President: Dr. Paul Neely, 1020 S. W. Taylor St., Portland.
Secretary-Treasurer: Dr. Lewis Jordon, 1020 S. W. Taylor St., Portland.
Place: Good Samaritan Hospital, Portland. Time: Third Tuesday of each month.

Pennsylvania Academy of Ophthalmology and Otolaryngology

President: Dr. Lewis T. Buckman, 83 S. Franklin St., Wilkes-Barre.
Secretary Pro Tem: Dr. Paul C. Craig, 232 N. 5th St., Reading.
Time: Last week in April.

Rhode Island Ophthalmological and Otological Society

Acting President: Dr. N. Darrell Harvey, 112 Waterman St., Providence.
Secretary-Treasurer: Dr. Linley C. Happ, 124 Waterman St., Providence.
Place: Rhode Island Medical Society Library, Providence. Time: 8:30 p. m., second Thursday in October, December, February and April.

South Carolina Society of Ophthalmology and Otolaryngology

President: Dr. J. L. Sanders, 222 N. Main St., Greenville.
Secretary: Dr. J. H. Stokes, 125 W. Cheves St., Florence.

Tennessee Academy of Ophthalmology and Otolaryngology

President: Dr. Wesley Wilkerson, 700 Church St., Nashville.
Secretary-Treasurer: Dr. W. D. Stinson, 124 Physicians and Surgeons Bldg., Memphis.

Texas Ophthalmological and Oto-Laryngological Society

President: Dr. F. H. Rosebrough, 603 Navarro St., San Antonio.
Secretary: Dr. M. K. McCullough, 1717 Pacific Ave., Dallas.

Utah Ophthalmological Society

President: Dr. R. B. Maw, 699 E. South Temple, Salt Lake City.
Secretary-Treasurer: Dr. Charles Ruggeri Jr., 1120 Boston Bldg., Salt Lake City.
Place: University Club, Salt Lake City. Time: 7:00 p. m., third Monday of each month.

Virginia Society of Oto-Laryngology and Ophthalmology

President: Dr. Mortimer H. Williams, 30½ Franklin Rd. S. W., Roanoke.
Secretary-Treasurer: Dr. Meade Edmunds, 34 Franklin St., Petersburg.

West Virginia State Medical Association, Eye, Ear, Nose and Throat Section

President: Dr. George Traugh, 309 Cleveland Ave., Fairmont.
Secretary: Dr. Welch England, 621½ Market St., Parkersburg.

LOCAL

Akron Academy of Ophthalmology and Otolaryngology

President: Dr. E. L. Mather, 39 S. Main St., Akron, Ohio.
Secretary-Treasurer: Dr. V. C. Malloy, 2d National Bank Bldg., Akron, Ohio.
Time: First Monday in January, March, May and November.

Atlanta Eye, Ear, Nose and Throat Society

President: Dr. B. M. Cline, 153 Peachtree St. N. E., Atlanta, Ga.
Acting Secretary: Dr. A. V. Hallum, 478 Peachtree St. N. E., Atlanta, Ga.
Place: Grady Hospital. Time: 6:00 p. m., fourth Monday of each month, from October to May.

Baltimore Medical Society, Section on Ophthalmology

Chairman: Dr. Ernst Bodenheimer, 1212 Eutaw Pl., Baltimore.
Secretary: Dr. Thomas R. O'Rourk, 104 W. Madison St., Baltimore.
Place: Medical and Chirurgical Faculty, 1211 Cathedral St. Time: 8:30 p. m., fourth Thursday of each month from October to March.

Birmingham Eye, Ear, Nose and Throat Club

President: Each member, in alphabetical order.
Secretary: Dr. Luther E. Wilson, 919 Woodward Bldg., Birmingham, Ala.
Place: Tutwiler Hotel. Time: 6:30 p. m., second Tuesday of each month, September to May, inclusive.

Brooklyn Ophthalmological Society

President: Dr. Michael J. Buonaguro, 589 Lorimer St., Brooklyn.
Secretary-Treasurer: Dr. Benjamin C. Rosenthal, 140 New York Ave., Brooklyn 16.
Place: Kings County Medical Society Bldg., 1313 Bedford Ave. Time: Third Thursday in February, April, May, October and December.

Buffalo Ophthalmologic Club

President: Dr. Walter F. King, 519 Delaware Ave., Buffalo.
Secretary-Treasurer: Dr. Sheldon B. Freeman, 196 Linwood Ave., Buffalo.
Time: Second Thursday of each month.

Chattanooga Society of Ophthalmology and Otolaryngology

President: Each member, in alphabetical order.
Secretary: Dr. Douglas Chamberlain, Chattanooga Bank Bldg., Chattanooga, Tenn.
Place: Mountain City Club. Time: Second Thursday of each month from September to May.

Chicago Ophthalmological Society

President: Dr. Vernon M. Leech, 55 E. Washington St., Chicago.
Secretary: Dr. W. A. Mann, 30 N. Michigan Ave., Chicago.
Place: Chicago Towers Club, 505 N. Michigan Ave. Time: Third Monday of each month from October to May.

Cincinnati General Hospital Ophthalmology Staff

Chairman: Dr. D. T. Vail, 441 Vine St., Cincinnati.
Secretary: Dr. A. A. Levin, 441 Vine St., Cincinnati.
Place: Cincinnati General Hospital. Time: 7:45 p. m., third Friday of each month except June, July and August.

Cleveland Ophthalmological Club

Chairman: Dr. Shandor Monson, 1621 Euclid Ave., Cleveland.
Secretary: Dr. Carl Ellenberger, 14805 Detroit Ave., Cleveland.
Time: Second Tuesday in October, December, February and April.

College of Physicians, Philadelphia, Section on Ophthalmology

Chairman: Dr. W. S. Reese, 1901 Walnut St., Philadelphia.
Clerk: Dr. George F. J. Kelly, 37 S. 20th St., Philadelphia.
Time: Third Thursday of every month from October to April, inclusive.

Columbus Ophthalmological and Oto-Laryngological Society

Chairman: Dr. H. D. Emswiler, 370 E. Town St., Columbus, Ohio.
Secretary-Treasurer: Dr. D. G. Sanor, 206 E. State St., Columbus, Ohio.
Place: The Neil House. Time: 6 p. m., first Monday of each month.

Corpus Christi Eye, Ear, Nose and Throat Society

Chairman: Dr. Arthur Padillo, 414 Medical Professional Bldg., Corpus Christi, Texas.
Secretary: Dr. Edgar G. Mathis, 815 Medical Arts Bldg., Corpus Christi, Texas.
Time: Second Friday of each month from October to May.

Dallas Academy of Ophthalmology and Oto-Laryngology

President: Dr. Ruby K. Daniel, Medical Arts Bldg., Dallas 1, Texas.
Secretary: Dr. Tom Barr, Medical Arts Bldg., Dallas 1, Texas.
Place: Dallas Athletic Club. Time: 6:30 p. m., first Tuesday of each month from October to June. The November, January and March meetings are devoted to clinical work.

Des Moines Academy of Ophthalmology and Otolaryngology

President: Dr. H. C. Schmitz, 604 Locust St., Des Moines, Iowa.
Secretary-Treasurer: Dr. Byron M. Merkel, 604 Locust St., Des Moines, Iowa.
Time: 7:45 p. m., third Monday of every month from September to May.

Detroit Ophthalmological Club

Chairman: Members rotate alphabetically.
Secretary: Dr. Cecil W. Lepard, 1025 David Whitney Bldg., Detroit.
Place: Club rooms of Wayne County Medical Society.
Time: First Wednesday of each month, November through April.

Detroit Ophthalmological Society

President: Dr. Parker Heath, 1553 Woodward Ave., Detroit.
Secretary: Dr. Leland F. Carter, 1553 Woodward Ave., Detroit.
Place: Club rooms of Wayne County Medical Society.
Time: Third Thursday of each month from November to April, inclusive.

Eastern New York Eye, Ear, Nose and Throat Association

President: Appointed at each meeting.
Secretary-Treasurer: Dr. Joseph L. Holohan, 330 State St., Albany.
Time: Third Wednesday in October, November, March, April, May and June.

Fort Worth Eye, Ear, Nose and Throat Society

President: Dr. Rex Howard, 602 W. 10th St., Fort Worth, Texas.
Secretary-Treasurer: Dr. R. H. Gough, Medical Arts Bldg., Fort Worth, Texas.
Place: Medical Hall, Medical Arts Bldg. Time: 7:30 p. m., first Friday of each month except July and August.

Houston Academy of Medicine, Ophthalmological and Oto-Laryngological Section

President: Dr. Lyle J. Logue, 1304 Walker Ave., Houston, Texas.
Secretary: Dr. John T. Stough, 803 Medical Arts Bldg., Houston, Texas.
Place: Medical Arts Bldg., Harris County Medical Society Rooms. Time: 8 p. m., second Thursday of each month from September to June.

Indianapolis Ophthalmological and Oto-laryngological Society

President: Dr. Myron Harding, 23 E. Ohio St., Indianapolis.
Secretary: Dr. Kenneth L. Craft, 23 E. Ohio St., Indianapolis.
Place: Indianapolis Athletic Club. Time: 6:30 p. m., second Thursday of each month from November to May.

Kansas City Society of Ophthalmology and Oto-Laryngology

President: Dr. Edgar Johnson, 906 Grand Ave., Kansas City, Mo.
Secretary: Dr. W. E. Keith, 1103 Grand Ave., Kansas City, Mo.
Time: Third Thursday of each month from October to June. The November, January and March meetings are devoted to clinical work.

Long Beach Eye, Ear, Nose and Throat Society

Chairman: Dr. Harold Snow, 614 S. Pacific Ave., San Pedro, Calif.
Secretary-Treasurer: Dr. Oliver R. Nees, 508 Times Bldg., Long Beach, Calif.
Place: Professional Bldg. Time: Last Wednesday of each month from October to May.

Los Angeles Society of Ophthalmology and Otolaryngology

President: Dr. M. E. Trainor, 523 W. 6th St., Los Angeles.
Secretary-Treasurer: Dr. Orrie E. Ghrist, 210 N. Central Ave., Glendale, Calif.
Place: Los Angeles County Medical Association Bldg., 1925 Wilshire Blvd. Time: 6:00 p. m., fourth Monday of each month from September to May, inclusive.

Louisville Eye and Ear Society

President: Dr. Joseph S. Heitger, Heyburn Bldg., Louisville, Ky.
Secretary-Treasurer: Dr. J. W. Fish, 321 W. Broadway, Louisville, Ky.
Place: Brown Hotel. Time. 6:30 p. m., second Thursday of each month from September to May, inclusive.

Lower Anthracite Eye, Ear, Nose and Throat Society

Chairman: Each member in alphabetical order.
Secretary: Dr. James J. Monohan, 31 S. Jardin St., Shenandoah, Pa.

Medical Society of the District of Columbia, Section of Ophthalmology and Otolaryngology

Chairman: Dr. P. S. Constantinople, 1835 I St. N. W., Washington.
Secretary: Dr. Frazier Williams, 1801 I St. N. W., Washington.
Place: 1718 M St. N.W. Time: 8 p.m., third Friday of each month from October to April, inclusive.

Memphis Society of Ophthalmology and Otolaryngology

Chairman: Each member in alphabetical order.
Secretary: Dr. Sam H. Sanders, 1089 Madison Ave., Memphis, Tenn.
Place: Eye Clinic of Memphis Eye, Ear, Nose and Throat Hospital. Time: 8 p.m., second Tuesday of each month from September to May.

Milwaukee Oto-Ophthalmic Society

President: Dr. Edwin C. Bach, 324 E. Wisconsin Ave., Milwaukee.
Secretary-Treasurer: Dr. Ralph T. Rank, 238 W. Wisconsin Ave., Milwaukee.
Place: University Club. Time: 6:30 p. m., second Tuesday of each month.

Montgomery County Medical Society

Chairman: Dr. H. V. Dutrow, 1040 Fidelity Medical Bldg., Dayton, Ohio.
Secretary-Treasurer: Dr. Maitland D. Place, 981 Reibold Bldg., Dayton, Ohio.
Place: Van Cleve Hotel. Time: 6:30 p. m., first Tuesday of each month from October to June, inclusive.

Montreal Ophthalmological Society

President: Dr. J. Rosenbaum, 1396 Ste. Catherine St. W., Montreal, Canada.
Secretary: Dr. L. Tessier, 1230 St. Joseph Blvd. E., Montreal, Canada.
Time: Second Thursday of October, December, February and April.

Nashville Academy of Ophthalmology and Otolaryngology

Chairman: Dr. M. M. Cullom, 700 Church St., Nashville, Tenn.
Secretary: Dr. R. E. Sullivan, 432 Doctors Bldg., Nashvile, Tenn.
Place: St. Thomas Hospital. Time: 8 p. m., third Monday of each month from October to May

New Haven Ophthalmological Society

President: Dr. William H. Ryder, 185 Church St. New Haven, Conn.
Secretary: Dr. Frederick A. Wiess, 255 Bradley St. New Haven, Conn.

New Orleans Ophthalmological and Oto-laryngological Society

President: Dr. W. B. Clark, 1012 American Bank Bldg., New Orleans.
Secretary: Dr. Mercer G. Lynch, 1018 Maison Blanche Bldg., New Orleans.
Place: Louisiana State University Medical Bldg. Time: 8 p. m., second Tuesday of each month from October to May.

New York Academy of Medicine, Section of Ophthalmology

Chairman: Dr. Thomas H. Johnson, 30 W. 59th St., New York.
Secretary: Dr. Wendell L. Hughes, 131 Fulton Ave., Hempstead, N. Y.
Time: 8:30 p. m., third Monday of every month from October to May, inclusive.

New York Society for Clinical Ophthalmology

President: Dr. Milton Berliner, 57 W. 57th St., New York.
Secretary: Dr. Benjamin Esterman, 983 Park Ave., New York.
Place: Squibb Hall, 745–5th Ave. Time: 8 p. m., first Monday of each month from October to May, inclusive.

Oklahoma City Academy of Ophthalmology and Otolaryngology

President: Dr. James P. Luton, 117 N. Broadway, Oklahoma City.
Secretary: Dr. Harvey O. Randel, 117 N. Broadway, Oklahoma City.
Place: University Hospital. Time: Second Tuesday of each month from September to May.

Omaha and Council Bluffs Ophthalmological and Oto-Laryngological Society

President: Dr. D. D. Stonecypher, Nebraska City, Neb.
Secretary-Treasurer: Dr. W. Howard Morrison, 1500 Medical Arts Bldg., Omaha.
Place: Omaha Club, 20th and Douglas Sts., Omaha. Time: 6 p. m. dinner; 7 p. m. program; third Wednesday of each month from October to May.

Passaic-Bergen Ophthalmological Club

President: Dr. Thomas Sanfacon, 340 Park Ave., Paterson, N. J.
Secretary-Treasurer: Dr. J. Averbach, 435 Clinton Ave., Clinton, N. J.
Place: Paterson Eye and Ear Infirmary. Time: 9 p. m., last Friday of every month, except June, July and August.

Philadelphia County Medical Society, Eye Section

President: Dr. Isaac Tassman, 136 S. 16th St., Philadelphia.
Secretary: Dr. Glen Gregory Gibson, 255 S. 17th St., Philadelphia.
Time: First Thursday of each month from October to May.

Pittsburgh Ophthalmological Society

President: Dr. George H. Shuman, 351-5th Ave., Pittsburgh.
Secretary: Dr. Robert J. Billings, 509 Liberty Ave., Pittsburgh.
Place: Pittsburgh Academy of Medicine Bldg. Time: Fourth Monday of each month, except June, July, August and September.

Reading Eye, Ear, Nose and Throat Society

President: Dr. Michael J. Penta, 312 N. 5th St., Reading, Pa.
Secretary: Dr. Paul C. Craig, 232 N. 5th St., Reading, Pa.
Place: Wyomissing Club. Time: 6:30 p. m., third Wednesday of each month from September to July.

Richmond Ophthalmological and Oto-Laryngological Society

President: Dr. Peter N. Pastore, Medical College of Virginia, Richmond, Va.
Secretary: Dr. Clifford A. Folkes, Professional Bldg., Richmond, Va.
Place: Westmoreland Club. Time: 6 p. m., second Monday of each month from October to May.

Rochester Eye, Ear, Nose and Throat Society

President: Dr. Frank Barber, 75 S. Fitzhugh St., Rochester, N. Y.
Secretary-Treasurer: Dr. Charles T. Sullivan, 277 Alexander St., Rochester, N. Y.

St. Louis Ophthalmic Society

President: Dr. C. C. Beisbarth, 3720 Washington Blvd., St. Louis.
Secretary: Dr. H. R. Hildreth, 508 N. Grand Blvd., St. Louis.
Place: Oscar Johnson Institute. Time: Clinical meeting, 5:30 p. m., dinner and scientific meeting 6:30 p. m., fourth Friday of each month from October to April, inclusive, except December.

San Antonio Ophthalmo-Oto-Laryngological Society

President: Dr. Belvin Pritchett, 705 E. Houston St., San Antonio 5, Texas.
Secretary-Treasurer: Lt. Col. John L. Matthews, AAF School of Aviation Medicine, Randolph Field, Texas.
Place: San Antonio, Brooke General Hospital, Randolph Field or San Antonio Aviation Cadet Center. Time: 7 p. m., second Tuesday of each month from October to May.

San Francisco County Medical Society, Section on Eye, Ear, Nose and Throat

Chairman: Dr. Roy H. Parkinson, 870 Market St., San Francisco.
Secretary: Dr. A. G. Rawlins, 384 Post St., San Francisco.
Place: Society's Bldg., 2180 Washington St., San Francisco. Time: Fourth Tuesday of every month except June, July and December.

Shreveport Eye, Ear, Nose and Throat Society

President: Dr. David C. Swearingen, Slattery Bldg., Shreveport, La.
Secretary-Treasurer: Dr. Kenneth Jones, Medical Arts Bldg., Shreveport, La.
Place: Shreveport Charity Hospital. Time: 7:30 p. m., first Monday of every month except July, August and September.

Spokane Academy of Ophthalmology and Oto-Laryngology

President: Dr. Clarence A. Veasey Sr., 421 W. Riverside Ave., Spokane, Wash.
Secretary: Dr. Clarence A. Veasey Jr., 421 W. Riverside Ave., Spokane, Wash.
Place: Spokane Medical Library. Time: 8 p. m., fourth Tuesday of each month except June, July and August.

Syracuse Eye, Ear, Nose and Throat Society

President: Dr. A. H. Rubenstein, 713 E. Genesee St., Syracuse, N. Y.
Secretary-Treasurer: Dr. I. H. Blaisdell, 713 E. Genesee St., Syracuse, N. Y.
Place: University Club. Time: First Tuesday of each month except June, July and August.

Toledo Eye, Ear, Nose and Throat Society

Chairman: Dr. E. W. Campbell, 316 Michigan St., Toledo, Ohio.
Secretary: Dr. L. C. Ravin, 316 Michigan St., Toledo, Ohio.
Place: Toledo Club. Time: Each month except June, July and August.

Toronto Academy of Medicine, Section of Ophthalmology

Chairman: Dr. W. R. F. Luke, 316 Medical Arts Bldg., Toronto, Canada.
Secretary: Dr. W. T. Gratton, 216 Medical Arts Bldg., Toronto, Canada.
Place: Academy of Medicine, 13 Queens Park. Time: First Monday of each month, November to April.

Washington, D. C., Ophthalmological Society

President: Dr. S. Bockoven, 1752 Massachusetts Ave., Washington, D. C.
Secretary-Treasurer: Dr. John Lloyd, 1218-16th St. N. W., Washington, D. C.
Place: Medical Society of District of Columbia Bldg., 1718 M St. N. W., Washington, D. C. Time: 7:30 p. m., first Monday in November, January, March and May.

Wilkes-Barre Ophthalmological Society

Chairman: Each member in turn.
Secretary: Dr. Samuel T. Buckman, 70 S. Franklin St., Wilkes-Barre, Pa.
Place: Office of chairman. Time: Last Tuesday of each month from October to May.